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NEWS  10 Jun 10  MEDLINE Reload
NEWS  11 Jun 10  BEILSTEIN has been reloaded
NEWS  12 Jul 02  FORGE no longer contains STANDARDS file segment
NEWS  13 Jul 22  WPAN to be reloaded July 26, 2002;
                 saved answer sets no longer valid
NEWS  14 Jul 29  Enhanced polymer searching in REGISTRY
NEWS  15 Jul 30  NETFIRST to be removed from STN
NEWS  16 Aug 05  CANCERLIT reload
NEWS  17 Aug 05  PHARMAMarketLetter(PHARMAML) - new on STN
NEWS  18 Aug 07  NTIS has been reloaded and enhanced
NEWS  19 Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                 now available on STN
NEWS  20 Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS  21 Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded
NEWS  22 Aug 26  Sequence searching in REGISTRY enhanced
NEWS  23 Sep 03  CAPIO has been reloaded and enhanced
NEWS  24 Sep 16  Experimental properties added to the REGISTRY file
NEWS  25 Sep 17  Indexing added to some pre-1967 records in CA/CAPLUS
NEWS  26 Sep 18  CA Section Thesaurus available in CAPLUS and CA
NEWS  27 Oct 01  CASREACT Enriched with Reactions from 1907 to 1985
NEWS  28 Oct 21  EVENTLINE has been reloaded
NEWS  29 Oct 24  BEILSTEIN adds new search fields
NEWS  30 Oct 24  Nutraceuticals International (NUTRACEUT) now available on STN
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=> s drug targeting
6 FILES SEARCHED...
L1 15,56 DRUG TARGETING

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L2 [illegible] L1 AND INTRACELLULAR

=> s l2 and protein
L3 [illegible] L2 AND PROTEIN

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PROCESSING COMPLETED FOR L3
L4 [illegible] DUP REMOVE L3 (42 DUPLICATES REMOVED)

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L5 [illegible] L4 AND PY<06

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L6 [illegible] DUP REMOVE L5 (0 DUPLICATES REMOVED)

=> d l6 1-5 cbib abs

L6 ANSWER 1 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002613605 EMBASE Identification of novel targets of immunosuppressive agents by cDNA-based microarray analysis. Crabtree A.D.; Bierer B.E.. B.E. Bierer, DHLBI, National Institutes of Health, Bldg. 10, 10 Center Dr., Bethesda, MD 20892, United States. bierer@nih.gov. Journal of Biological Chemistry 277/6 (4465-4476) 8 Feb 2002.
Refs: 76.
ISSN: 0021-9258. CODEN: JBCHA3. Pub. Country: United States. Language:

English. Summary Language: English.

AB The immunosuppressive agents cyclosporin A (CsA) and tacrolimus (**FK506**) bind to unrelated **intracellular** immunophilin receptors, cyclophilin (CyP) and **FK506**-binding **protein** (FKBP), respectively. The complexes of CsA.cyclophilin.CyP and of **FK506**.cyclophilin.FKBP both bind to and inhibit the activity of the calcium calmodulin-dependent serine threonine phosphatase calcineurin. We used cDNA microarray analysis to characterize early human peripheral blood T cell transcriptional responses following antigen receptor stimulation in the absence or presence of CsA or **FK506**, hoping to identify novel targets dependent upon calcineurin or immunophilins or, perhaps, specific targets of either CyP or FKBP inhibitable by one drug alone. The array data failed to identify genes uniquely sensitive to only one drug, suggesting that transcriptionally regulated, immunophilin-dependent but calcineurin-independent targets fell below the limits of detection in this system. In contrast, transcript profiling identified and mRNA and **protein** analysis confirmed novel as well as known genes reproducibly induced or inhibited by both immunosuppressive agents. In this context, we show that transcriptional activation of Stat5a and repression of the cytokine interleukin-16 are regulated by T cell receptor engagement and dependent upon drug-immunophilin complexes and, presumably, calcineurin activity.

L6 ANSWER 4 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

20022077716 EMBASE New compounds for the treatment of eczematous skin diseases. Worm M., Dr. M. Worm, Universitatsklinikum Charite, Klin. Dermatol. Venerol. Allergol., Schumannstr. 20-21, 10117 Berlin, Germany. margitta.worm@charite.de. Expert Opinion on Therapeutic Patents 12/7 (1133-1141) 2002.

Refs: 54.

ISSN: 1354-3776. CODEN: EOTPEJ. Publ. Country: United Kingdom. Language: English. Summary Language: English.

AB Eczematous skin diseases, like atopic dermatitis and contact dermatitis have been treated with topical glucocorticosteroids for decades. With the introduction of the immunophyllins **FK506** and ascomycin, a new treatment era has begun. The increasing knowledge of pathophysiological interactions and immunological disturbances during the chronic inflammatory process in the skin offers many new therapeutical approaches. These are presented in this review, based on the status of recent patents. Novel therapeutical compounds include cytokine antagonists, cytokine-receptor antagonists, but also molecules interfering with signal transduction pathways. Such molecules inhibit certain **intracellular** signal transducing phosphatases or act at the molecular level of transcription factors. Recent developments target lymphocyte homing through interference of adhesion molecules and chemokine / chemokine receptors. The diversity of these interactions is extensive and clinical trials will unravel their clinical efficacy. Finally, the developments of glucocorticoid family members, such as retinoids, vitamin D and peroxisome proliferator activated receptor agonists, are discussed. Molecules from members of this family have profound differentiating, antiproliferative, but also immunomodulatory effects, which make them attractive as anti-eczematous compounds. The design of molecules with high selectivity or in combination formulae highlight them as molecules of interest".

L6 ANSWER 5 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

20010079299 EMBASE Human epidermal Langerhans' cells are targets for the immunosuppressive macrolide tacrolimus (**FK506**). Panhans-Gross A.; Novak N.; Kraft S.; Bieber T., Dr. T. Bieber, Department of Dermatology, Friedrich-Wilhelms-University, Sigmund-Freud-Str 25, D-53105 Bonn, Germany. Journal of Allergy and Clinical Immunology 107/2 (345-352) 2001.

Refs: 46.

ISSN: 0091-6749. CODEN: JACIBY. Pub. Country: United States. Language: English.. Summary Language: English.

AB Background: The immunosuppressive macrolide tacrolimus (**FK506**) has been shown to inhibit allergic contact dermatitis in animal models as well as in human beings. More recently, successful treatment of atopic dermatitis with an ointment containing tacrolimus has been reported. Objectives: We explored the effects of this compound on epidermal Langerhans' cells (LCs), which are known to play an important pathophysiologic role in inflammatory skin diseases. Methods: The expression of the **intracellular FK506** binding **protein** (FKBP12) was monitored on freshly isolated and cultured epidermal LCs. Phenotypic and functional exploration of LCs treated with different concentrations of tacrolimus and .beta.-methasone valerate (.beta.Mv) were performed. Results: FKBP12 is expressed in freshly isolated LCs but is lost while they are maturating into mature dendritic cells. Tacrolimus inhibited the expression of IL-2R, CD69, and of the costimulatory molecules CD80 (B7.1) and CD40. Expression of MHC class I and II was also affected, whereas CD86 (B7.2) expression was not altered. In contrast, .beta.Mv strongly increased the expression of CD25. Paradoxically, while decreasing CD40 and MHC class I expression, .beta.Mv significantly increased the expression of MHC class II, CD80, and CD86 on cultured LCs but impaired their allostimulatory activity. Tacrolimus was about 100 times more potent than .beta.Mv at inhibiting LC stimulatory function. Conclusion: Tacrolimus can exert immunopharmacologic alterations in LCs, which may account, at least in part, for the therapeutic effect of this compound in eczematous skin diseases.

L6 ANSWER 4 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2000:07167 EMBASE **FK506**, an immunosuppressant targeting calcineurin function. Dumont F.J., F.J. Dumont, Department of Immunology, Merck Research Laboratories, Rahway, NJ 07065, United States. Current Medicinal Chemistry 7,7 (731-748) 2000.

Refs: 210.

ISSN: 0929-8673. CODEN: CMCHE7. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB The macrolactam natural product, **FK506** (Tacrolimus), acts as a powerful and clinically useful immunosuppressant through disruption of signaling events mediated by the calcium dependent serine threonine **protein** phosphatase, calcineurin (CaN), in T lymphocytes. Its mechanism of action involves the formation of a molecular complex with the **intracellular FK506**-binding **protein**-12 (FKBP12), thereby acquiring the ability to interact with CaN and to interfere with its access to and dephosphorylation of various substrates. Among the CaN substrates whose activity is altered by **FK506**, the nuclear factors of activated T cells (NFAT), a family of transcription factors regulating lymphokine gene expression have been shown to play a prominent role in **FK506**-induced immunosuppression. Over the past few years, additional members of the FKBP and NFAT families of **proteins** have been identified, providing further insights into the complexity of **FK506** biological effects. Furthermore, it has become clear that, predominantly as a result of CaN inhibition, **FK506** alters multiple biochemical processes in a variety of cells besides lymphocytes. This may account for the adverse side effects of the drug, including neurotoxicity and nephrotoxicity. Extensive medicinal chemistry effort have been devoted to the generation of analogs of **FK506** with the hope of identifying compounds with an improved therapeutic index, that could have broader therapeutic utility than the parent drug. These efforts yielded several compounds with unique biochemical attributes, showing evidence for a dissociation between immunosuppressive and toxic properties, which may pave the way towards designing safer **FK506**-related immunosuppressants.

L6 ANSWER 5 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

97005382 EMBASE Document No.: 1997005382. The immunosuppressant **FK506** and its nonimmunosuppressive analog L- 685,818 are toxic to Cryptococcus neoformans by inhibition of a common target **protein**. Odom A.; Del Poeta M.; Perfect J.; Heitman J.. J. Heitman, 322 CARL Bldg., Duke University Medical Center, Box 3546, Research Dr., Durham, NC 27710, United States. Antimicrobial Agents and Chemotherapy 41/1. (156-161) 1997.
Refs: 42.
ISSN: 0066-4804. CODEN: AMACCQ. Pub. Country: United States. Language: English.. Summary Language: English..

AB The immunosuppressant **FK506** (tacrolimus) is an antifungal natural product macrolide that suppresses the immune system by blocking T-cell activation. In complex with the **intracellular protein** FKBP12, **FK506** inhibits calcineurin, a Ca2+-calmodulin-dependent serine-threonine **protein** phosphatase. We recently reported that growth of the opportunistic fungal pathogen Cryptococcus neoformans is resistant to **FK506** at 24.degree.C but sensitive at 37.degree.C and that calcineurin, the target of FKBP12-FK506, is required for growth at 37.degree.C in vitro and pathogenicity in vivo. These findings identify calcineurin as a potential antifungal drug target. In previous studies the calcineurin inhibitor cyclosporin A (CsA) was effective against murine pulmonary infections but exacerbated cryptococcal meningitis in rabbits and mice, largely because CsA does not cross the blood-brain barrier. Although we find that **FK506** penetrates the CNS, **FK506** also exacerbates cryptococcal meningitis in rabbits. Thus, **FK506** immunosuppression outweighs antifungal action in vivo. Like **FK506**, the nonimmunosuppressive **FK506** analog L-685,818 is toxic to C. neoformans in vitro at 37.degree.C but not at 24.degree.C, and **FK506**-resistant mutants are resistant to L-685,818, indicating a similar mechanism of action. Fluconazole-resistant C. neoformans clinical isolates were also found to be susceptible to both **FK506** and L-685,818. Our findings identify calcineurin as a novel antifungal drug target and suggest the nonimmunosuppressive **FK506** analog L-685,818 or other congeners warrant further consideration as antifungal drugs for C. neoformans.

=> s FK506 conjugate
L7 10 FK506 CONJUGATE

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PROCESSING COMPLETED FOR L7
L8 6 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> d l8 1-6 cbib abs

L8 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2002 ACS
2002:31414 Document No. 136:53220 Yeast three-hybrid system for in vivo drug screening and enzyme evolution using chemical inducers of dimerization. Cornish, Virginia W. (USA). U.S. Pat. Appl. Publ. US 2001042067 A1 20011108, 48 pp., Cont.-in-part of U.S. Ser. No. 490,320. (English). CODEN: USXXCO. APPLICATION: US 2001-776,479 20010204. PRIORITY: US 2000-490320 20000124.

AB The disclosed invention relates to the evolution of enzymes in vivo, and drug screening in vivo through the use of chem. inducers of protein dimerization. The subject invention provides a compd. having the formula: H1-X--B-Y--H2 wherein each of H1 and H2 may be the same or different and capable of binding to a receptor which is the same or different; wherein each of X and Y may be present or absent and if present, each may be the same or different spacer moiety; and wherein B is an enzyme cleavable moiety. This invention also provides a method of screening proteins for the ability to catalyze bond cleavage or bond formation, comprising the steps of: (a) providing a cell that expresses a pair of fusion proteins

which upon dimerization change a cellular readout; (b) providing the compd. of the invention which dimerizes the pair of fusion proteins, said compd. comprising two portions coupled by a bond that is cleavable or formed by the protein to be screened; and (c) screening for the cellular readout, wherein a change the cellular readout indicates catalysis of bond cleavage or bond formation by the protein to be screened. However, it has not heretofore been suggested to use small mol. induced protein dimerization to screen for catalysis in vivo, and specifically, it has not been suggested to use an enzyme cleavable moiety to link two mols. to dimerize proteins. This invention provides proteins de novo with prescribed binding and catalytic properties and permits screening cDNA libraries based on biochem. function. Practically, we believe that powerful screens in combination with existing randomization techniques will make it possible to take an existing protein fold and evolve it into an enzyme with a new function generating useful catalysts for the pharmaceutical and chem. industries. Since the screen is done in vivo and in both prokaryotes and eukaryotes, the method. can be applied to functional genomics and drug discovery. A new chem. inducer of dimerization (CID) was recently developed in Professor Crabtree's lab, which uses a heterodimer of methotrexate (MTX) and dexamethasone (DEX) which, when placed in the yeast three-hybrid system, reconstitutes transcription of the lacZ gene. The effects of altering the structure of the DEX-MTX CID and the protein chimeras in the three-hybrid assay were investigated. It was found. that all DEX-MTX CIDs, except the DEX-MTX CID with the shortest chem. linker, showed the ability to induce .beta.-galactosidase levels at levels 40× above strains possessing no CID. The DEX-MTX CIDs showed little or no increase in .beta.-galactosidase levels above background levels in strains where dihydrofolate reductase (DHFR from E. coli was replaced by DHFR from murine. The three-hybrid system did show some directional preference to the way in which the receptors where fused to the DNA binding domain and the activation domain. These studies have led to a better understanding of the factors that are important in activating transcription in the DEX MTX yeast three-hybrid system.

L8 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS

2001:9144[illegible] Document No. 134:150472 Synthetic transcriptional modulator ligands and their use in gene regulation with chimeric proteins containing DNA-binding domains and ligand-binding domains. Verdine, Gregory L.; Nyanguile, Origene (President and Fellows of Harvard College, USA). U.S. US 6,833,269 B1 20011204, 33 pp., Cont.-in-part of U.S. Ser. No. 487,812. (English). CODEN: USXXAM. APPLICATION: US 1488-20F057 19[illegible]. PRIORITY: US 1447-[illegible] 19971203.

AB Novel synthetic transcriptional modulators having at least one selected ligand linked to at least one transcriptional modulating portion are described. The transcriptional modulators of the present invention can include a ligand linked to a chem. moiety. These transcriptional modulators can be used to selectively control gene expression and to identify components of the transcriptional machinery. Thus, the covalent conjugate (designated L-1) of FK506 and a 28-amino acid peptide of herpes simplex virus VP16 activator domain stimulates transcription in the presence of the chimeric GAL4-FKBP protein, but was unable to stimulate in the absence of GAL4-FKBP and the activation potential was significantly reduced in the presence of added rapamycin or SDZ-FKBP. Since cyclic peptides having the natural L stereochem. configuration are highly susceptible to proteolysis, the analogous conjugate (D-1) bearing nonnatural D stereochem. is prepd. D-1 reproducibly stimulated transcription to a significant extent, though to a slightly lesser extent than L-1. The synthesis of a combinatorial compd. library is also provided, and various library components are active transcriptional modulators when coupled to the HATU analog of FK506.

L8 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2002 ACS

2000:116960 Document No. 132:171072 Conjugates targeted to target receptors and/or interleukin-2 receptors. Prakash, Ramesh K.; Clemens, Christopher M. Watson Laboratories, Inc. (Utah, USA). PCT Int. Appl. WO 2000007549 A2 20000217, 67 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 1999-US17645 19990804. PRIORITY: US 1998-132972 19980804.

AB A compn. for intracellular delivery of a chem. agent into a target receptor and/or interleukin-2-receptor-bearing cell, e.g. an activated T cell and cancer cell, includes a chem. agent, at least one copy of a target-receptor binding and/or an interleukin-2-receptor-binding and endocytosis-inducing ligand coupled to a water sol. polymer. The ligand binds to a target receptor and/or IL-2 receptor on the target receptor and/or IL-2-receptor-bearing cell and elicits endocytosis of the compn. The compn. also optionally includes a biodegradable spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. The compn. can further comprise a carrier such as another water sol. polymer, liposome, or particulate. Methods of using these compns. for delivering a chem. agent in vivo or in vitro are also disclosed. A method of detecting a disease, such as cancer, T-cell lymphocytic leukemia, T-cell acute lymphoblastic leukemia, peripheral T-cell lymphoma, Hodgkin's disease, and non-Hodgkin's lymphoma, assocd. with elevated levels of sol. target receptor and or IL-2 receptor is also disclosed.

L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2000 ACS

1998:83774 Document No. 130:158406 Development of a macromolecular prodrug of FK506: 1. Synthesis of FK506-dextran conjugate. Yura, H.; Yoshimura, N.; Hamashima, T.; Oka, T.; Tanaka, Y.; Hashida, M. (Department of Drug Delivery Research, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan). Transplantation Proceedings, 30(7), 3495-3499 English 1998. CODEN: TRPPA4. ISSN: 0041-1345. Publisher: Elsevier Science Inc..

AB Activated tacrolimus FK506-succinate and dextran conjugates were prepd. as prodrugs via coupling reaction..

L8 ANSWER 5 OF 6 MEDLINE DUPLICATE

97262261 Document Number: 97262261. PubMed ID: 9198651. Tacrolimus (FK506): validation of a sensitive enzyme-linked immunosorbent assay kit for and application to a clinical pharmacokinetic study. Lee T W; Rukovaty R L; Farmer R H; Dressler D E; Alak A; Bekersky I. (Harris Laboratories, Lincoln, Nebraska 68501, USA.) THERAPEUTIC DRUG MONITORING, (1997 Apr) 19 (2) 171-7. Journal code: 7910660. ISSN: 0163-4356. Pub. country: United States. Language: English.

AB Tacrolimus (FK506) is a macrolide immunosuppressant approved for the prophylaxis of organ rejection in liver transplant. Immunoassays of low intra- and interday variability and high sensitivity are necessary to adequately characterize terminal elimination phase concentrations in pharmacokinetic studies. A new ELISA kit for the quantitation of tacrolimus in human whole blood has been validated for use in pharmacokinetic studies. Methanol sample extracts were dried and reconstituted in a horseradish peroxidase (HPR)-**FK506 conjugate** solution. The reconstituted samples and mouse anti-FK506 were added to a microplate, precoated with secondary antibody, and incubated, FK506 and the HPR-**FK506 conjugate** competed

to bind with anti-FK506, which was immobilized by binding to the secondary antibody. Unbound FK506 was washed away, and substrate was added for color development. Once the reaction was stopped with 2 N H_2SO_4, the plate was read at 450 nm. The linear range was 0.1-60 ng/ml, with a limit of quantitation of 0.5 ng/ml. Interday precision and accuracy were < or = 10.4% C.V. and < or = 5% R.E. for quality control samples. The lack of interference from endogenous compounds was established by parallelism and recoveries of FK506 from six lots of control matrix. Cross-reactivity against the metabolites and analogs were not performed because the kit monoclonal antibody was from the same source as Kobayashi et al (1). The utility and sensitivity of the kit present a good method for the quantitation of tacrolimus in blood from pharmacokinetic studies. The method is robust and has been used to assay tacrolimus in several thousand whole blood samples by multiple analysts.

L8 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2002 ACS
1994:648878 Document No. 121:248278 Blood cells or blood cell fragments in stable aqueous FK506 standards for FK506 diagnostic analysis. Grenier, Frank C.; Dlaczkiw, Julie A.; Bergmann, Kerry E.; Blonski, David R. (Abbott Laboratories, USA). U.S. US 5314834 A 19940816, 8 pp. Cont. of U.S. Ser. No. 712,410, abandoned. English. CODEN: USXXAM. APPLICATION: US 1993-71941 19930608. PRIORITY: US 1991-712410 19910611.
AB A stabilized, aq. compn. contg. FK506 is disclosed for diagnostic assays for FK506. FK506 degrades rapidly in most aq. matrixes. The rate of degrdn. is decreased in the presence of whole blood cells or fragments of blood cells from human or animal sources. A no. of matrixes using blood components are possible. Blood can be used directly or the blood cells can be lysed. The blood is dild. with a soln. of an alkali halide.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:37:46 ON 04 NOV 2002
L1 15246 S DRUG TARGETING
L2 811 S L1 AND INTRACELLULAR
L3 81 S L2 AND PROTEIN
L4 79 DUP REMOVE L3 (2 DUPLICATES REMOVED)
L5 8 S L4 AND FK506
L6 8 DUP REMOVE L5 (0 DUPLICATES REMOVED)
L7 11 S FK506 CONJUGATE
L8 6 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> s l4 and conjugate
L9 L4 AND CONJUGATE

=> s l4 and conjugate
L10 39 L4 AND CONJUGATE

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PROCESSING COMPLETED FOR L10
L11 39 DUP REMOVE L10 (0 DUPLICATES REMOVED)

=> d l11 1-39 cbib abs

L11 ANSWER 1 OF 39 CAPLUS COPYRIGHT 2002 ACS
2002:621523 Document No. 137:173175 Adrenergic receptor ligand-neurotoxin **conjugates** and methods for treating pain. Gil, Daniel W.; Aoki, Kei Roger (Allergan Sales, Inc., USA). PCT Int. Appl. WO 2002053177 A2 20020711, 76 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,

ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. English . CODEN: PIXXD2. APPLICATION: WO 2001-US48651 20011214. PRIORITY: US 2000-75054 20001229.

AB Agents for treating pain, methods for producing the agents, and methods for treating pain by administration to a patient of a therapeutically effective amt. of the agent, are disclosed. The agent may include a clostridial neurotoxin, a fragment or a deriv. thereof, attached to a targeting component, wherein the targeting component is selected from a group consisting of compds. which selectively binds to the alpha-2b or alpha-2 alpha-2c adrenergic receptor subtype as compared to other binding sites, e.g. the alpha-2a adrenergic receptor subtype.

L11 ANSWER 3 OF 19 MAPLUS COPYRIGHT 2002 ACS

2002:91446 Document No. 137:8144 Imidazole and thiazolederivatives and compounds in treatment for inhibiting neoplastic lesions and microorganisms. Shanahan-Bonenberger, Elizabeth Irene. PCT Int. Appl. WO 2002-IB2831 AL 20020711, 69 pp. DESIGNATED STATES: W: AE, AG, AT, AU, BB, BG, BR, BY, CA, CH, CN, CO, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IB2831 20020711. PRIORITY: IE 2001-2 20010102.

AB The invention discloses the use of imidazole and/or thiazolederivatives, deriv., metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immunodysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasitic agents, radiation and/or surgery. Imidazole and thiazolederivatives and their mixt. showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

L11 ANSWER 4 OF 19 MAPLUS COPYRIGHT 2002 ACS

2002:49562 Document No. 137:50121 Compounds for **intracellular** delivery of therapeutic moieties to nerve cells. Hill, Gordon Craig; Kohl, Stephen B.; Webb, Robert; McKee, Constance A. Mayo Corporation, USA). PCT Int. Appl. WO 2001-US20620, 47 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. English . CODEN: PIXXD2. APPLICATION: WO 2001-US20620 20010627. PRIORITY: US 2000-214051 20000627.

AB A method for improving intracellular administration of a therapeutic agent is provided, comprising: contacting cells with a compd. comprising a charged deriv. of a therapeutic agent having a therapeutic activity, the charged deriv. being conjugated to a **protein** having a biol. activity of being transported across a cell membrane into a cell; and having the cell transport the compd. into the cell where the cell metabolizes at least a portion of the compd. to form a charged metabolite product that possesses the therapeutic activity of the therapeutic agent, the charged metabolite product being less prone to being transported across the cell membrane out of the cell relative to the compd. and less prone to being transported across the cell membrane out of the cell relative to the therapeutic agent.

L11 ANSWER 5 OF 19 MAPLUS COPYRIGHT 2002 ACS

2002:39781 Document No. 136:156599 Polymer-based **intracellular**

delivery system for **protein** phosphatases and other **proteins** and therapeutic uses thereof. Lavi, Sara; Satchi-Fainaro, Ronit (Ramot-University Authority for Applied Research and Industrial Development Ltd., Israel . PCT Int. Appl. WO 2002007671 A2 20020131, 73 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. English. CODEN: PIXXD2. APPLICATION: WO 2001-IL6[illegible] 20010726. PRIORITY: US 2000-PV220871 20000726; US 2000-[illegible]87.[illegible] 2[illegible]0[illegible]22.

AB This invention provides a polymer-based **intracellular** delivery system for **protein** phosphatases and other polypeptides. This delivery system can be used to deliver polypeptides for anti-tumor, anti-inflammatory, or immunosuppressive therapy, for treatment of genetic disorder or disease, and for therapy of any condition which requires **intracellular** delivery of polypeptides. Preferred embodiments according to the invention utilize acrylamide based polymers, most preferably copolymers comprising hydroxypropyl methacrylamide.

L11 ANSWER 5 OF [illegible] CAPLUS COPYRIGHT 2[illegible] ACS
2002:[illegible] Document No. 136:[illegible] Polymer-based **intracellular** delivery system for **protein** phosphatases and uses thereof in tumor therapy. Lavi, Sara; Satchi-Fainaro, Ronit (Ramot-University Authority for Applied Research and Industrial Development Ltd., Israel). PCT Int. Appl. WO [illegible] A2 [illegible]0131, [illegible] pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. English. CODEN: PIXXD2. APPLICATION: WO 2001-IL[illegible] 20010726. PRIORITY: US 2000-PV220[illegible] 20000726; US 2000-[illegible].4 2000[illegible].

AB The invention provides **protein** and cDNA sequences of two novel human **protein** phosphatase 2Cs, designated as **protein** phosphatase 2C.zeta. and 2C.eta.. The invention also provides a polymer-based **intracellular** delivery system for **protein** phosphatases using hydroxypropyl methacrylamide (HPMA) copolymers. This delivery system can be used to deliver **protein** phosphatases for any disease or disorder in which it is desirable to elevate **protein** phosphatase activity, particularly for tumor therapy.

L11 ANSWER 6 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002[illegible] EMBASE A doxorubicin-CNGRC-peptide **conjugate** with prodrug properties. Van Hensbergen Y.; Broxterman H.J.; Elderkamp Y.W.; Lankelma J.; Beers J.C.C.; Heijn M.; Boven E.; Hoekman K.; Pinedo H.M.. H.J. Broxterman, Department of Medical Oncology, Vrije Universiteit Medical Centre, P.O. Box 7057, 1007 MB, Amsterdam, Netherlands. h.broxterman@vumc.nl. Biochemical Pharmacology [illegible] /5 (897-908) 1 Mar 2002.
Refs: 40.
ISSN: 0006-2952. CODEN: BCPCA6.
Publisher Ident.: S 0006-2952(01)00928-5. Pub. Country: United States.
Language: English. Summary Language: English.

AB There is increasing interest in the exploitation of molecular addresses for the targeting of tumor imaging or therapeutic agents. A recent study demonstrated anticancer activity in human xenografts of doxorubicin (DOX)-peptide **conjugates** targeted to the tumor vascular

endothelium, among them DOX coupled to the cyclic pentapeptide CNGRC [Science 279 (1998) 377]. In order to learn more about the mechanism of action of this type of DOX-peptide **conjugates**, we have studied the interaction of DOX-CNGRC with primary human umbilical cord vein endothelial cells (HUVEC) and tumor cells under defined in vitro conditions. We used a DOX **conjugate**, in which the cyclic CNGRC peptide, for which an in vivo endothelial address has recently been identified as aminopeptidase N (APN) CD13, has been coupled via a hydrolysable spacer to the C-14 anthracycline-side chain. First we determined that the t1/2 of DOX-CNGRC **conjugate** in human blood was 44.2min (at 37.degree.) allowing sufficient time for endothelial targeting when administered i.v. When cultured cells were exposed for 1 min to DOX-CNGRC a more cytoplasmic localization of fluorescent drug was seen when compared to DOX exposure and **intracellular** DOX-CNGRC was identified after extraction from the cells. This revealed differences in the cellular uptake process of the **conjugate** compared to DOX. The antiproliferative effect of DOX-CNGRC was determined by 1 min exposure in medium with a high **protein** content in order to mimick the in vivo targeting situation. In this medium, the IC(50) was 1.1.mu.M for highly CD13 expressing HT 1080, 1.45.mu.M for CD13 negative MES-SA-1 sarcoma cells and 0.5.mu.M for CD13 positive HUVEC. The IC(50) of DOX for these cells were 1.0, 2.7 and 0.3.mu.M, respectively. Although DOX-CNGRC inhibited the peptidase activity of CD13 up to 50%, our data do not favor an important role for the enzyme inhibition in the cytotoxic effect of the **conjugate**. The antitumor activity was tested in nude mice bearing human ovarian cancer xenografts (OVCAR-3). A weekly i.v. administration (5mg/kg DOX-equivalent, 3x) showed a tumor growth delay, which does not indicate efficacy better than that expected for free DOX. In conclusion, this study indicates that the antiproliferative and anti-angiogenic effects of DOX-CNGRC as reported before, are likely caused by the cytostatic effects of intracellularly released parent drug DOX, independent of CD13 expression activity. More research is needed to identify the optimal spacer-linker configuration of DOX-peptide **conjugates** for in vivo targeting and receptor mediated cellular uptake. .COPYRGT. 2002 Elsevier Science Inc. All rights reserved.

L11 ANSWER 7 OF 34 SCISEARCH COPYRIGHT 2002 ISI (R)

2002:63153 The Genuine Article (R) Number: 513DT. Folate-mediated delivery of macromolecular anticancer therapeutic agents. Lu Y J; Low P S (Reprint). Purdue Univ, Dept Chem, 1393 Brown Bldg, W Lafayette, IN 47907 USA (Reprint); Purdue Univ, Dept Chem, W Lafayette, IN 47907 USA. ADVANCED DRUG DELIVERY REVIEWS, 15 SEP 2001, Vol. 54, No. 5, pp. 675-693. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0169-409X. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE HELP AND IASL FORMATS

AB The receptor for folic acid constitutes a useful target for tumor-specific drug delivery, primarily because: (1) it is upregulated in many human cancers, including malignancies of the ovary, brain, kidney, breast, myeloid cells and lung, (2) access to the folate receptor in those normal tissues that express it can be severely limited due to its location on the apical (externally facing) membrane of polarized epithelia, and (3) folate receptor density appears to increase as the stage/grade of the cancer worsens. Thus, cancers that are most difficult to treat by classical methods may be most easily targeted with folate-linked therapeutics. To exploit these peculiarities of folate receptor expression, folic acid has been linked to both low molecular weight drugs and macromolecular complexes as a means of targeting the attached molecules to malignant cells. Conjugation of folic acid to macromolecules has been shown to enhance their delivery to folate receptor-expressing cancer cells in vitro in almost all situations tested. Folate-mediated macromolecular targeting in vivo has, however, yielded only mixed results, largely because of problems with macromolecule penetration of solid tumors. Nevertheless, prominent examples do exist where folate targeting

has significantly improved the outcome of a macromolecule-based therapy, leading to complete cures of established tumors in many cases. This review presents a brief mechanistic background of folate-targeted macromolecular therapeutics and then summarizes the successes and failures observed with each major application of the technology.

L11 ANSWER 8 OF 39 CAPLUS COPYRIGHT 2002 ACS
2001:816499 Document No. 135:357735 Membrane-permeant peptide complexes for medical imaging, diagnostics, and pharmaceutical therapy. Piwnica-Worms, David (Washington University, USA). PCT Int. Appl. WO 2001082975 A2 20011108, 77 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. English. CODEN: PIXXD2. APPLICATION: WO 2001-US13179 20010424. PRIORITY: US 2000-567465 20000425.

AB Methods and compns. for medical imaging, evaluating **intracellular** processes and components, radiotherapy of **intracellular** targets, and drug delivery by the use of novel cell membrane-permeant peptide **conjugate** coordination and covalent complexes having target cell specificity are provided. Kits for conjugating radionuclides and other metals to peptide coordination complexes are also provided.

L11 ANSWER 9 OF 39 CAPLUS COPYRIGHT 2002 ACS
2001:635415 Document No. 135:176400 Membrane estrogen receptor-directed therapy in breast cancer. Pietras, Richard J.; Marquez-Garban, Diana C. (Regents of the University of California, USA). PCT Int. Appl. WO 2001062288 A1 20010830, 82 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. English. CODEN: PIXXD2. APPLICATION: WO 2001-US5197 20010222. PRIORITY: US 2000-PV185026 20000225.

AB Methods of diagnosing and treating mammalian tumors with molS. including anti-estrogen receptor Ig polypeptides are provided. In an illustrative embodiment, anti estrogen receptor Ig polypeptides specific to distinct epitopes of the ligand-binding domain of estrogen receptor are contacted with membrane-assocd. estrogen receptor under conditions which allow binding of the anti-estrogen receptor Ig polypeptide to a degree sufficient to inhibit tumor growth by inhibiting the activation of the membrane-assocd. estrogen receptor. Injectable compns. for treating certain mammalian tumors with monoclonal antibodies and methods for diagnosing mammalian cancers which express an estrogen receptor assocd. with the surface membrane of the cells are also disclosed. Further, alternate methods for blocking **intracellular** signal transduction emanating from the activation of membrane-assocd. estrogen receptor forms are also presented. These approaches also appear sufficient to inhibit tumor growth.

L11 ANSWER 10 OF 39 CAPLUS COPYRIGHT 2002 ACS
2001:618026 Document No. 135:180444 **Conjugates** targeted to target receptors. Prakash, Ramesh K.; Anderson, Christopher G. (Watson Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 2001060848 A1 20010823, 94 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE,

GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE, SN, TD, TG, US. English . CODEN: PIXXD2. APPLICATION: WO 2001-US5115 . 01-0215. PRIORITY: US 2000-507140 2000 . 18.

AB A **conjugate** for **intracellular** delivery of a chem. agent into a target receptor such as an interleukin-2-receptor-bearing cell, e.g., an activated T cell and cancer cell, includes a chem. agent, at least one copy of target-receptor binding and endocytosis-inducing ligand coupled to a water sol. polymer. The ligand binds to a target receptor such as an IL-2 receptor on the target receptor-bearing cell and elicits endocytosis of the **conjugate**. The **conjugate** also optionally includes a biodegradable spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. Methods of using these conjugates for delivering a chem. agent in vivo or in vitro are also disclosed. Methods of detecting a disease, such as cancer, T-cell lymphocytic leukemia, T-cell acute lymphoblastic leukemia, peripheral T-cell lymphoma, Hodgkin's disease, and non-Hodgkin's lymphoma, assocd. with elevated levels of a cell target receptor and or IL-2 receptor are also disclosed.

L11 ANSWER 11 OF 39 CAPLUS COPYRIGHT 2002 ACS
2001:17[illegible] Document No. 134:[illegible] Epitopes formed by multivalent association of **conjugates**. Nagy, Roger; Toth, Istvan Pharmacia UK Limited, UK). PCT Int. Appl. WO 2001011440 A1 20 .0114, 34 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE, SN, TD, TG. English . CODEN: PIXXD2. APPLICATION: WO 2000-GB3469 20000627. PRIORITY: GB 1999-15074 19990628.

AB A compn. for interacting with a ligand, which compn. comprises a non-covalent assocn. of a plurality of distinct **conjugates**, each **conjugate** comprising a head group and a tail group, wherein the tail groups of the **conjugates** form a hydrophobic aggregation and the **conjugates** are movable within the assocn. so that, in the presence of a ligand, at least two of the head groups are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of head groups individually. The invention aims to overcome the problems involved in the development of **protein** receptor specific therapeutic **conjugates** that includes evoking immune response or attacking by endopeptidases. The **conjugates** comprise a head group of amino acid, peptide, monosaccharide, polysaccharide, nucleotide, polynucleotide, steroid, water-sol. vitamin, porphyrin, metal ion chelate, water-sol. drug, hormone, enzyme substrate; a spacer of hydroxy acid, amino acid, sugar or polyethylene glycol; and a tail group of branched-chain fatty acid, alc., aldehyde, prostaglandin, leukotriene, glyceride, sphingosine, ceramide, silicon or deriv.

L11 ANSWER 1. OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
2001:162712 The Genuine Article (R) Number: 400LX. Cell-selective **intracellular** delivery of a foreign enzyme to endothelium in vivo using vascular immunotargeting. Scherpereel A; Wiewrodt R; Christofidou-Solomidou M; Germais R; Murciano J C; Albelda S M; Muzykantov V R (Reprint). Univ Penn, Med Ctr, Inst Environm Med, 1 John Morgan Bldg,

36th St & Hamilton Walk, Philadelphia, PA 19104 USA (Reprint); Univ Penn, Med Ctr, Inst Environm Med, Philadelphia, PA 19104 USA; Univ Penn, Med Ctr, Dept Med, Pulm Allergy & Crit Care Div, Philadelphia, PA 19104 USA; Univ Penn, Med Ctr, Dept Pharmacol, Philadelphia, PA 19104 USA. FASEB JOURNAL (FEB 2001) Vol. 15, No. 2, pp. 416-426. Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. ISSN: 0892-6638. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND CALL FORMATS

AB Vascular immunotargeting, the administration of drugs conjugated with antibodies to endothelial surface antigens, has the potential for drug delivery to the endothelium. Our previous cell culture studies showed that biotinylated antibodies to PECAM-1, a highly expressed endothelial surface antigen, coupled with streptavidin-SA, a cross-linking **protein** that facilitates anti-PECAM internalization and targeting, may provide a carrier for the **intracellular** delivery of therapeutic enzymes. This paper describes the PECAM-directed vascular immunotargeting of a reporter enzyme (beta-galactosidase, beta-Gal) in intact animals. Intravenous injection of [I-125]SA-beta-Gal conjugated with either anti-PECAM or IgG had a high I-125 uptake in liver and spleen, yet beta-Gal activity in these organs rapidly declined to the background levels, suggesting rapid degradation of the **conjugates**. In contrast, anti-PECAM [I-125]SA-B-Gal, but not IgG [I-125]SA beta-Gal, accumulated in the lungs (6.0+/-1.3 vs. 0.4+/-0.6 injected dose %) and induced a marked elevation of beta-Gal activity in the lung tissue persisting for up to 8 h after injection (10-fold elevation 4 h postinjection). Using histochemical detection, the beta-Gal activity in the lungs was detected in the endothelial cells of capillaries and large vessels. The anti-PECAM carrier also provided I-125 uptake and beta-Gal activity in the renal glomeruli. Predominant **intracellular** localization of anti-PECAM/SA-beta-Gal was documented in the PECAM-expressing cell in culture by confocal microscopy and in the pulmonary endothelium by electron microscopy. Therefore, vascular immunotargeting is a feasible strategy for cell-selective, **intracellular** delivery of an active foreign enzyme to endothelial cells in vivo, and thus may be potentially useful for the treatment of acute pulmonary or vascular diseases.

L11 ANSWER 13 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
2001277011 EMBASE Sterically stabilized polyplex: ligand-mediated activity.
Woodle M.C.; Pedaria P.; Ganesan S.; Subramanian K.; Titmus B.; Cheng C.; Yang J.; Pan Y.; Wang M.; Su J.; Torrelson S.; M.C. Woodle, Intradigm Corporation, 6405 Beech Tree Road, Bethesda, MD 20817, United States. mwoodle@intradigm.com. Journal of Controlled Release 74 1-3 (309-311) 6 Jul 2001.
Refs: 5.
ISSN: 0168-3659. CODEN: JCREEC.
Publisher Ident.: S 0168-3659(01)00339-X. Pub. Country: Netherlands.
Language: English. Summary Language: English.

AB Synthetic vectors have been considered as a safer and more versatile alternative to viral-based gene delivery systems. A variety of very simple synthetic vector systems, e.g., cationic lipid- and polymer-complexed plasmid DNA have activity in vivo but it appears to be mediated by non-specific electrostatic interactions limiting targeting. In order to avoid these problems, we designed a sterically stabilized layered colloidal system. The steric polymer coating relates non specific interactions. We have synthesized a PEG **conjugate** of PEI that complexes DNA to form small, stable colloids with a steric polymer coat on their surface. The polymer enhances colloidal stability and reduces non-specific binding and toxicity. It also renders the complex inactive presumably due to reduced binding. Ligands are then appended to the distal end of the steric polymer to restore cell binding and expression at target cells. We prepared **conjugates** with RGD peptide ligands appended to the distal end of the steric polymer. The resulting **conjugates** also form complexes but with ligands exposed on their surface restoring

binding and activity. Labeled oligonucleotides and DNA were used to measure **intracellular** distribution. Oligonucleotides are found localized in the nucleus, whereas the labeled plasmid DNA remained in the cytoplasm. Import of plasmid DNA into the nucleus appears to be very inefficient yet sufficient for expression. .COPYRGT. 2001 Elsevier Science B.V. All rights reserved.

L11 ANSWER 14 OF 39 CAPLUS COPYRIGHT 2001 ACS
2000:814264 Document No. 133:366416 Nucleic acid-antibody **conjugate** for delivering a foreign nucleic acid in cells. Hirsch, Francois; Duerbach, Antoine (Centre National de la Recherche Scientifique CNRS), Fr. . PCT Int. Appl. WO 2000067807 A2 20001116, 48 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. (French). CODEN: PIXXD2. APPLICATION: WO 2000-FR1113 20000428. PRIORITY: FR 1999-5194 19990429.
AB The invention concerns the technique related to the insertion of foreign nucleic acids in cells. More particularly, it concerns a DNA-antibody **conjugate** enabling an efficient foreign DNA expression in vivo or in vitro in **protein** form in target cells.

L11 ANSWER 15 OF 39 CAPLUS COPYRIGHT 2001 ACS
2000:177838 Document No. 132:190167 Photosensitizer **conjugates** for targeting **intracellular** pathogens. Hasan, Tayyaba; Gross, Zeev; Nau, Gerard J. (The General Hospital Corporation, USA). PCT Int. Appl. WO 2000012131 A1 20000309, 85 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. English. CODEN: PIXXD2. APPLICATION: WO 1999-US19124 19990825. PRIORITY: US 1998-PV97494 19980826; US 1999-PV115976 19990114.
AB Methods are provided to treat mycobacterial infections, or any disease or disorder that is caused or aggravated by an **intracellular** pathogen. The method(s) of the invention involves administering to a subject, a mol. **conjugate** that includes a photosensitizer (a light-activatable compd. and a targeting moiety, the targeting moiety being capable of targeting the **conjugate** to the **intracellular** pathogen.

L11 ANSWER 16 OF 39 CAPLUS COPYRIGHT 2001 ACS
2000:17861 Document No. 132:88838 Anti-microbial targeting for **intracellular** pathogens. Horwitz, Marcus A.; Clements, Daniel L. (The Regents of the University of California, USA). U.S. US 6054138 A 20000425, 11 pp. English. CODEN: USXXAM. APPLICATION: US 1997-990858 19971210.
AB A method and compns. are provided for treating **intracellular** pathogens that reside in phagosomes. The compns. include antibiotics which are conjugated with transferrin or other ligands to form **conjugates** that target membrane-bound pathogens. The **conjugates** are selectively taken up by infected phagocytes. **Conjugates** are provided which utilize transferrin as the targeting ligand for treating mycobacterium which reside in membrane-bound phagosomes. To demonstrate that exogenously administered transferrin is delivered to the M. tuberculosis phagosome, human monocyte-derived macrophages were coincubated with Mycobacterium tuberculosis and polystyrene beads. The infected macrophages were cultured for 3 days in an RPMI contg. heat inactivated-fetal bovine serum. The macrophages were pulsed for inactivated-fetal bovine serum. The macrophages were pulsed for 0-60 min with human holo-transferrin (1 mg/mL), fixed, and cryosectioned, and the sections stained specifically for human transferrin

using immunogold. In control macrophages, not incubated with human transferrin, only 7% of M. tuberculosis phagosomes stained for transferrin, a level consistent with the background level of staining.

L11 ANSWER 17 OF 39 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000361126 EMBASE Synthesis, characterisation and in vivo behaviour of a norfloxacin-poly(L-lysine citramide imide) **conjugate** bearing mannosyl residues. Gad S.; Couvreur P.; Benoit M.; Domurado M.; Vert M.; P. Couvreur, CNRS UPRESA 8076, Faculty of Pharmacy, Montpellier I University, 15 Ave. Charles Flahault, 34060 Montpellier cedex 2, France. pcouvreu@pharma.univ-mont.pl.fr. Journal of Drug Targeting 7 6 (393-406) 2000.
Refs: 17.
ISSN: 1061-186X. CODEN: JDTABH. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB With the aim of promoting the targeting of macrophage mannose receptors and the internalization of the norfloxacin antibiotic, which is active against some **intracellular** bacteria, a macromolecular prodrug was synthesized where the antibiotic and mannosyl moieties were coupled to a polymeric carrier, namely poly(L-lysine citramide imide). This carrier, which derived from two metabolites, citric acid and L-lysine, is known to be biocompatible and slowly degradable under slight acidic conditions. Norfloxacin was coupled onto the acid groups present along the polymer chains, and **conjugates** were characterised by UV, TLC and SEC. The mannosyl groups selected to promote the targeting of the mannose-specific lectin present on the outer membrane of macrophages were incorporated through a biodegradable glycolic spacer arm. Two different strategies were considered to synthesize the full **conjugates**, namely coupling norfloxacin onto mannosylated **conjugates**, and coupling mannose onto FLAIM-Mtx **conjugates**. The second pathway led to better results regarding mannosylation. The presence of norfloxacin and mannose carbon chain aggregation, especially for **conjugates** with a high content of mannosyl residues. The targeting ability of the prodrug was investigated using a method based on the competition between the mannosylated macromolecules and glucose oxidase, a mannosyl-bearing non human **protein**. This method showed that prodrug macromolecules competed effectively with glucose oxidase and thus should be able to bring the drug up to the mannosyl receptor bearing membranes of macrophages infected by **intracellular** bacteria.

L11 ANSWER 18 OF 39 JAPIO COPYRIGHT 2002 JPO
2000:151715 Document No. 12-151715 Trials of molecular targeting to overcome multidrug resistance. Ohkawa, Hiyomi (Dep. Biochem., The Jikei Univ. Sch. Med., Japan). Tokyo Jikeikai Ika Daigaku Zasshi, 115(1), 1-9 (Japanese) 2000. CODEN: TTIDAH. ISSN: 0171-9172. Publisher: Tokyo Jikeikai Ika Daigaku Zeikkai.
AB A review with 30 refs. Two methods have been proposed to overcome multidrug resistance (MDR). One method is drug modification to escape the p-glycoprotein (Pgp) pump mechanism. Doxorubicin (DXR) conjugated to **proteins** (such as serum albumin, transferrin, and IgG) via the glutaraldehyde bridge showed **intracellular** drug-accumulation without active efflux and exhibited potent dose-dependent inhibition of cell growth against MDR tumor cells and their parent cells. In addn., tumor-bearing rats receiving the **protein**-DXR **conjugate** survived significantly longer than did control rats or rats receiving DXR alone. These results indicate that chem. modification allows DXR to escape from the MDR mechanism. Careful anal. of active adducts derived from **protein**-DXR **conjugates** showed that reduced glutathione (GSH) was an appropriate partner for conjugation with DXR. The GSH-DXR **conjugate** accumulated at high levels in cells and induced potent apoptosis with activation of caspase-3, but not caspase-1, at much lower concns. than DXR. Another proposed method of overcoming MDR is to regulate Pgp-degrdn. and thereby efficiently control mol.

functions. When calpain, a calcium-activated neutral protease, was inhibited in MDR cells with high Pgp expression, the accumulation of ubiquitinated Pgp was detectable at the cell surface with retardation of Pgp turnover. In such cases, despite the increased accumulation of Pgp mols. at the cell surface after treatment with a calpain inhibitor, the cytoplasmic DNR level of cells treated with a calpain inhibitor was higher than that of untreated cells and approached that of parental, drug-sensitive cells. These findings indicate that Pgp mols. accumulating at the cell surface membrane after calpain inhibition are mostly inactive and will decrease in function, thereby causing the 170-kDa mature Pgp to be degraded after entering the endocytic pathway. These phenomena suggest that modulation of Pgp turnover made be another method of overcoming MDR.

L11 ANSWER 1 OF 39 CAPLUS COPYRIGHT 2002 ACS
1999:81[illegible]4.7 Document No. [illegible]:6..e7 Membrane-permeant peptide complexes for medical imaging, diagnostics, and pharmaceutical therapy. Frankel-Worms, David (Washington University, USA . PCT Int. Appl. W 9967[illegible]4 A. [illegible]9991224, 65 pp. DESIGNATED STATES: W: AB, AL, AM, AT, AU, AZ, BA, BB, BG, BF, BY, CA, CH, CN, CR, CU, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. English . CODEN: PIXXD2. APPLICATION: W[illegible]-99-US1[illegible]60 19990[illegible]. PRIORITY: US 1998-[illegible]7 1998[illegible]2.

AB Methods and compns. for medical imaging, evaluating **intracellular** processes and components, radiotherapy of **intracellular** targets, and drug delivery by the use of novel cell membrane-permeant peptide **conjugate** coordination and covalent complexes having target cell specificity are provided. Kits for conjugating radionuclides and other metals to peptide coordination complexes are also provided.

L11 ANSWER 2 OF 39 CAPLUS COPYRIGHT 2002 ACS
1999:[illegible]99[illegible] Document No. [illegible]:2[illegible]29 Methods and reagents for targeting organic compounds to selected cellular locations. Farinas, Javier (The Regents of the University of California, USA . PCT Int. Appl. W[illegible] 9951986 A1 [illegible]9991[illegible]14, 69 pp. DESIGNATED STATES: W: AB, AL, AM, AT, AU, AZ, BA, BB, BG, BA, BY, CA, CH, CN, CR, CU, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. English . CODEN: PIXXD2. APPLICATION: W[illegible]-99-US[illegible]47 1999[illegible]08. PRIORITY: US 1998-[illegible]113 1998[illegible]08; US 1998-[illegible]40 1998[illegible]09.

AB The present invention provides methods and reagents for targeting probes to selected cellular locations, through the expression of specific binding partners to that probe within the cell. In one embodiment, the probes may comprise spectroscopic probes that can be used in a method for localizing a specific binding partner within a cell, and for creating assays for post-translational activities. The invention allows the monitoring of the location of such **intracellular** specific binding partners over time and in response to stimuli, such as test chems. The spectroscopic probes can be used for screening a test chem. for activity. The present invention also includes cells and transgenic organisms comprising the **intracellular** specific binding partner, wherein the specific binding partner can bind with the spectroscopic probe ligand **conjugate**. CHO cells were transfected with cDNAs encoding single chain antibody (sFv) fusion proteins with a Golgi-targeting human .beta.-1,4-galactosyltransferase segment. The sFv bound to hapten 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (phOx) fluorescein **conjugate**. The Golgi-targeted phOx-fluorescein was used to detect

continuous changes in lumenal pH in individual cells.

L11 ANSWER 11 OF 39 CAPLUS COPYRIGHT 2002 ACS
1999:59499. Document No. 131:144114 Biotin-streptavidin conjugated antibodies for enhancement of **intracellular** delivery and tissue targeting of drugs and genes. Muzykantov, Vladimir R.; Albelda, Steven M. (The Trustees of the University of Pennsylvania, USA). PCT Int. Appl. WO 9945970 A1 19990916, 33 pp. DESIGNATED STATES: W: AU, CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. English. CODEN: PIXXD2. APPLICATION: WO 1999-US5279 19990310. PRIORITY: US 1998-PV77375 19980310.

AB A method for enhancing **intracellular** delivery of effector mols. is provided. The method involves modifying selected antibodies with biotin and streptavidin, conjugating these antibodies with an effector mol., and delivering the conjugated effector to an **intracellular** target specifically recognized by the antibody.

L11 ANSWER 12 OF 39 CAPLUS COPYRIGHT 2002 ACS
1999:49547 Document No. 130:122626 Antibody receptor targeting moiety for enhanced delivery of armed ligand. Burton, Jack; Goldenberg, David M. (Center for Molecular Medicine and Immunology, USA). PCT Int. Appl. WO 9904817 A1 19990204, 47 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 1998-US15113 19980724. PRIORITY: US 1997-53682 19970725.

AB A method for **intracellular** delivery of drugs or other agents for diagnosis and therapy of malignancies or immune-mediated or inflammatory conditions. A targeting moiety of an antibody and the ligand binding region of a selected cytokine receptor is used. The targeting moiety targets surface antigen on a specific cell population. The targeting moiety is administered to a subject, and then, after a specified interval, therapeutic or diagnostic agents linked to the cognate cytokine are given. The invention provides rapid, efficient internalization of the cytokine receptor antibody antigen complexes. Targeting of a high-level cell surface antigen with such bispecific fusion mols. substantially increases the no. of cytokine receptors over their low background level. Thus, bifunctional sol. fusion **protein** IL-13R.alpha.-MN-14 scFv comprising interleukin 13 receptor .alpha. chain and anti-CEA antibody was prepd. and used with radiolabeled IL-13 or IL-13 onconase immunotoxin for therapy of colon, lung, breast, pancreatic, gastric, ovarian and medullary thyroid carcinoma.

L11 ANSWER 13 OF 39 CAPLUS COPYRIGHT 2002 ACS
1999:176818 Document No. 130:247179 **Conjugates** targeted to the interleukin-2 receptor. Pravasth, Ramesh K. (Theratech, Inc., USA). PCT Int. Appl. WO 9914214 A2 19990318, 51 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 1997-US15229 19970805. PRIORITY: US 1997-914042 19970805.

AB A compn. for **intracellular** delivery of a chem. agent into an interleukin-2-receptor-bearing cell, e.g. an activated T cell, includes a chem. agent and at least two copies of an interleukin-2-receptor-binding and endocytosis-inducing ligand coupled to a water sol. polymer. The

ligand binds to a receptor on the interleukin-2-receptor-bearing cell and elicits endocytosis of the compn. The compn. also optionally includes a spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. The compn. can further comprise a carrier such as another water sol. polymer, liposome, or particulate. Methods of using these compns. for delivering a chem. agent in vivo or in vitro are also disclosed.

L11 ANSWER 24 OF 39 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
19982407609 EMBASE Conjugation of 5-fluoro-2'-deoxyuridine with lactosaminated poly-L-lysine to reduce extrahepatic toxicity in the treatment of hepatocarcinomas. Di Stefano G.; Bucci C.; Lenzini M.; Tiezzi D.; Fiume L., Prof. L. Fiume, Dipartimento Patologia Sperimentale, Via San Giacomo 14, 40126 Bologna, Italy. lfiume@kaiser.alma.unibo.it. Italian Journal of Gastroenterology and Hepatology 30:3 (173-177) 1998.
Refs: 29.
ISSN: 1121-760X. CODEN: IJGAFI. Pub. Country: Italy. Language: English. Summary Language: English.
AB Background. The hepatocyte receptor for asialoglycoproteins, which binds and internalizes galactosyl-terminating peptides, was found to be expressed also on the cells of well differentiated hepatocarcinomas. Aims. We explored the possibility of obtaining a delivery of antiblastic drugs to hepatocarcinoma cells through this receptor. Methods. We conjugated 5-fluoro-2'-deoxyuridine (FUDR) with lactosaminated poly-L-lysine. 5-fluoro-2'-deoxyuridine is an active drug in the treatment of solid tumours, but with toxic effects on intestine and bone marrow. Poly-L-lysine is an galactosyl-terminating carrier which enables preparation of **conjugates** with very high drug load. We studied the pharmacological activity of poly-L-lysine-5-fluoro-2'-deoxyuridine **conjugate** on in vitro proliferation of Hep G2 cells, a human hepatocarcinoma cell line. Moreover, we compared the levels of radioactivity in liver, intestine and heart of mice injected with free or conjugated [^{3}H,5-fluoro-2'-deoxyuridine. Results. We found that poly-L-lysine-5-fluoro-2'-deoxyuridine enters into Hep G2 cells through the asialoglycoprotein receptor and, after **intracellular** penetration, releases the drug in a pharmacologically active form. Administered to mice, the **conjugate** leads to enhanced accumulation of the drug in liver versus the intestine and the heart. Conclusions. These data support conjugation with poly-L-lysine as a way to obtain **drug targeting** to those hepatocellular carcinomas which maintain the asialoglycoprotein receptor.

L11 ANSWER 25 OF 39 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
19982810049 EMBASE Controlling liposome blood clearance by surface-grafted polymers. Woodle M.C., M.C. Woodle, Genetic Therapy, Inc., 968 Clopper Rd., Gaithersburg, MD 20878, United States. Advanced Drug Delivery Reviews 32:1-2 (139-152) 5 Jun 1998.
Refs: 139.
ISSN: 0169-409X. CODEN: ADDREP.
Publisher Ident.: S0169-409X(97)00136-1. Pub. Country: Netherlands.
Language: English. Summary Language: English.
AB The incorporation of polymer-lipid **conjugates**, initially using PEG and subsequently other selected flexible, hydrophilic polymers, into lipid bilayers gives rise to sterically stabilized liposomes that exhibit reduced blood clearance and concomitant changes in tissue distribution largely because of reduced, but not eliminated, phagocytic uptake. Changes in tissue distribution includes 'passive' targeting localization into sites of tumors, infection, inflammation characterized by presence of a 'leaky' vasculature which represent useful applications for drug delivery. The polymer forms a surface coating which has been characterized by

physical measurements and it appears to function through steric inhibition of the **protein** binding and cellular interactions leading to phagocytic uptake. The current understanding of the physical and biological properties are reviewed. Ongoing work in the field involves interests to increase complexity such as addition of (1) selective targeting ligands by chemical conjugation to the exterior surface of the polymer coating, (2) capabilities for **intracellular** release of encapsulated agents into the cytoplasm, and (3) both simultaneously.

L11 ANSWER 26 OF 29 CAPLUS COPYRIGHT 2002 ACS
1997:436044 Document No. 127:55402 Tumor-associated internalizing antigens and methods for targeting therapeutic agents. Huse, William D.; Watkins, Jeffry D. (Ixsys, Incorporated, USA). PCT Int. Appl. WO 9717998 A1 19970522, 41 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. English. ODDEN: PIXXD2. APPLICATION: WO 1996-US18121 19961111. PRIORITY: US 1995-556684 19951111.

AB Proliferation of neoplastic cells is inhibited by contacting the cells with a cytotoxic or cytostatic binding agent (conjugated e.g. to an antibody) specifically reactive with an aberrantly expressed vesicular membrane-associated neoplastic cell-specific internalizing antigen selected from the Lamp-1 and Lamp-II families of lysosomal integral membrane **proteins**. A method of **intracellular** targeting of a cytotoxic or cytostatic agent to a neoplastic cell population consists of administering a cytotoxic or cytostatic binding agent specifically reactive with an aberrantly expressed vesicular membrane associated neoplastic cell-specific internalizing antigen that is expressed by the neoplastic cell population, wherein the cytotoxic or cytostatic binding agent is bound by the neoplastic cell-specific internalizing antigen and is internalized into the **intracellular** compartment.

L11 ANSWER 27 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97083171 EMBASE Document No.: 1997083171. **Intracellular** routing and inhibitory activity of oligonucleopeptides containing a KDEL motif. Pichon C.; Arar K.; Stewart A.F.; Dodon M.D.; Gaudin L.; Courtoy P.J.; Mayer R.; Monsigny M.; Roche A.-C., A.-C. Roche, Glycobiologie CBM-CNRS, rue Charles Sadron, F-45071 Orleans Cedex 02, France. roche@cnrs-orleans.fr. Molecular Pharmacology 51 2 (431-443) 1997.
Refs: 38.
ISSN: 0026-895X. CODEN: MOPMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB On internalization, oligonucleotides (ODN) remain mostly sequestered in endocytic compartments. To increase their delivery into the cytosol and/or nucleus, which contain their targets, we attempted to guide them into compartments containing the KDEL receptor. Antisense ODN, phosphodiester protected at both ends, that are complementary to the AUG initiation site of gag(HIV-1) mRNA (odn) were linked to a peptide ending with the Lys-Asp-Glu-Leu (KDEL) motif in a carboxyl-terminal position (odn-p-KDEL) or with the Lys-Asp-Glu-Ala (odn-p-KDEA) as a control. The effect of odn substitution with a peptide was examined with regard to its accumulation, subcellular location, and activity in HepG2 cells. Although odn-p-KDEL was internalized 4-fold less than the corresponding peptide-free odn, it was 5-fold more efficient in inhibiting gag(HIV-1) gene expression in HepG2 cells. The internalization of odn-p-KDEA was as low as that of odn-p-KDEL, but its biological activity was lower, close to that of the peptide-free odn. In endocytosis at 37.degree., both **conjugates** as well as the peptide-free odn were found in a neutral environment. However, the substitution of an odn with a KDEL motif altered its **intracellular** trafficking; most of the odn-p-KDEL was found in the endoplasmic reticulum

and in the intermediate compartment as identified by colabeling with either anti-ERGIC-53 or anti-KDEL receptor antibodies. Conversely, hdn-p-KDEA and peptide-free hdn were localized in vesicular compartments not labeled with these antibodies. In addition, pulse-chase experiments showed that hdn-p-KDEL and hdn-p-KDEA had a lower efflux than peptide-free hdn. Therefore, the large increase in efficiency was due to the KDEL motif.

L11 ANSWER 33 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
1998:12663 The Genuine Article (R) Number: ZK063. Poly(ethylene glycol)-grafted liposome therapeutics. Woodle M C (Reprint). GENET THERAPY INC, 928 DOTTER RD, GAITHERSBURG, MD 20878 (Reprint). ACS SYMPOSIUM SERIES (FEB 1998) Vol. 680, pp. 49-61. Publisher: AMER CHEMICAL SOC, 1155 SIXTEENTH ST NW, WASHINGTON, DC 20036. ISSN: 0097-6156. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB PEG-lipid **conjugates** have been synthesized and incorporated into liposomes to form a steric polymer surface barrier that enhances drug delivery applications. The PEG steric coating reduces **protein** binding, cellular recognition, and uptake. Thus these liposomes persist in the blood permitting extravasation into tumors, infections, and sites of inflammation. Thus PEG-grafted liposome formulations can deliver encapsulated drugs to these pathological sites, shown with doxorubicin treatment of tumors and Kaposi's Sarcoma. Other drugs are being evaluated in PEG-grafted liposome drug formulations to take advantage of this form of ''passive'' targeting. Additionally, efforts are being applied to obtain ligand-mediated targeting or ligand presentation through chemical conjugation to the exterior surface of the PEG coating. Improved **drug targeting** and use for gene therapy, which requires **intracellular** delivery, are limited by a need to control tissue distribution separately from drug release or cellular interactions.

L11 ANSWER 34 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
96:576857 The Genuine Article (R) Number: VC745. MEASUREMENT OF ENDOSOME PH FOLLOWING FOLATE RECEPTOR-MEDIATED ENDOCYTOSIS. LEE R J; WANG S; LOW P S (Reprint). PURDUE UNIV, DEPT CHEM, 1393 BROWN BLDG, W LAFAYETTE, IN, 47907 (Reprint); PURDUE UNIV, DEPT CHEM, W LAFAYETTE, IN, 47907. BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH 24 JUL 1996 Vol. 1312, No. 3, pp. 237-242. ISSN: 0167-4889. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Free folic acid is believed to enter some cells by folate receptor-mediated endocytosis at membrane invaginations termed caveolae. Folate conjugated macromolecules also enter cells by folate receptor-mediated endocytosis, but their site of entry has never been conclusively identified. In this paper, we show that internalization of folate-macromolecule **conjugates** by receptor-bearing KB cells can be blocked by agents that specifically inhibit caveolae assembly or internalization such as nystatin and phorbol-12-myristate acetate (PMA). To characterize the **intracellular** conditions to which the macromolecule-folate **conjugates** are subsequently exposed, we have measured the pH of the major compartments of the folate endocytosis pathway. pH values of individual endosomal compartments in KB cells were determined by dual-excitation laser-scanning confocal microscopy, where the fluorescence ratio of folate-DM-NERF-dextran (pH-sensitive) and Texas Red-dextran (pH-insensitive) was used to calculate pH. These studies revealed that the pH of folate **conjugate**-containing endosomes commonly varies between 4.7 and 5.6, with the pH in some endosomes as low as 4.3. The most frequent pH value in these compartments was similar to 5.2.

L11 ANSWER 35 OF 39 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
96157946 EMBASE Document No.: 1996157946. Targeting growth factor receptors with bispecific molecules. Mokotoff M.; Chen J.; Zhou J.-H.; Ball E.D..

School of Pharmacy, Dept. of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA 15261, United States. Current Medicinal Chemistry 2 2 (87-100) 1995.
ISSN: 0929-8673. CODEN: CMCHE7. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB Peptide growth factor receptors on the surface of malignant cells bind to their ligands with high affinity, resulting in **intracellular** responses which cause differentiation, growth, and the survival of these cells. Peptide growth factors, or monoclonal antibodies (mAbs) which target growth factor receptors, have been conjugated to drugs, toxins, radionuclides, or other MAbs that recognize activate effector cells which can phagocytose or kill. These types of conjugated products, which have the ability to kill malignant cells, we call bispecific molecules (BsMol) and is the basis of this review article. The growth factors/receptors covered include .alpha.- and .beta.-melanocyte stimulating hormone (MSH), bombesin/gastrin releasing peptide (BN/GRP), epidermal growth factor (EGF), HER-2 neu oncogene **protein** p185(HER2), interleukin-2, and somatostatin. The preparation and biological use/activity of the following BsMol are discussed: .beta.-MSH-daunomycin, [Nle4, D Phe7]MSH-anti-CD3, 111In-DTPA-bis-.alpha.-MSH, DAB389-MSH, mAb12-Lys-BN, mAb12-Antenn, anti-EGFR/anti-CD3, DOXEB2, DAB389EGF, 111In-DTPA-T25, anti-p185 HER2 - SAI, 2B1, MDX-210, rumAb4D5 x rumAb520HT1, DAB4-61L-2, 111In-DTPA-octreotide (OctreoScan.RTM.), DX-88-NGF, and DTA03-2.

L11 ANSWER 31 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
95204214 EMBASE Document No.: 1995204214. Receptor-mediated delivery of p-aminosalicylic acid conjugated to maleylated serum albumin against Mycobacterium tuberculosis infection in guinea pigs. Majumdar S.; Basu S.K.. Institute Microbial Technology, Chandigarh 160 014, India. Drug Delivery: Journal of Delivery and Targeting of Therapeutic Agents 2 2 (141-145) 1995.
ISSN: 1071-7544. CODEN: DDELE6. Pub. Country: United States. Language: English. Summary Language: English.

AB We have previously reported that the scavenger receptor-mediated uptake of para-aminosalicylic acid (PAS) conjugated to maleylated bovine serum albumin (MBSA) resulted in elimination of **intracellular** Mycobacterium tuberculosis (MTB) in mouse peritoneal macrophages in culture (Majumdar, S., and Basu, S. K. (1991) Antimicrob. Agents Chemother. 35, 1785-1791). In this paper, we report therapeutic efficacy of PAS-MBSA **conjugate** in vivo against MTB infection in guinea pigs. Two or 4 intravenous (iv) injections of PAS-MBSA **conjugate** weekly led to a greater reduction in the number of bacteria in the lung, liver, and spleen of the infected animals than the reduction caused by free PAS. PAS-MBSA treatment also increased the survival rate of the infected animals. High and persistent drug activity was observed in the target organs when the drug was delivered as PAS-MBSA **conjugate**. The superior efficacy of PAS-MBSA is presumably due to selective delivery of the **conjugate** to the macrophages, resulting in enhanced **intracellular** availability of the drug.

L11 ANSWER 32 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
94340277 EMBASE Document No.: 1994340277. Targeting enzymes for cancer therapy: Old enzymes in new roles. Denekamp M.P.; Epenetos A.A.. Tumour Targeting Laboratory, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS, United Kingdom. British Journal of Cancer 70 (Dec. '94) 1044.
ISSN: 0007-0920. CODEN: BJCAAI. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Enzymes which traditionally have played no role in cell-directed cytotoxicity are finding their way into schemes for prodrug activation and immunotoxin owing to such useful enzymatic activity. Alkaline phosphatase, carboxypeptidases, .beta.-glucosidases and .beta.-lactamases among many others are being utilised to regenerate potent anti-cancer

drugs or toxic small molecules from precursors in a bid to enhance their activity in tumours. These prodrug activation systems require the pretargeting of the enzyme to the surface of a tumour cell, usually by an antibody or its immunoreactive fragment. A recent novel approach proposes the **intracellular** delivery of appropriate enzymes, such as phosphodiesterases, to particular cellular compartments. There, enzyme activity can cause substantive damage resulting in cell death. Cell targeting of mammalian phosphodiesterases promises to improve upon conventional immunotoxins because of their increased cytotoxicity when targeted to the appropriate compartment and their expected lack of, or lower, immunogenicity in clinical use.

L11 ANSWER 33 OF 33 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
93079[illegible] EMBASE Document No.: 1993 [illegible]. The current status of immunotoxins: An overview of experimental and clinical studies as presented at the third international symposium on immunotoxins. Vallera D.A.; Frankel A.. University of Minnesota, Box 356 UMHC, 420 Delaware Street SE,Minneapolis, MN 55455, United States. Leukemia 7/3 (641-648) 1993. ISSN: 0887-6924. CODEN: LEUKEM. Pub. Country: United Kingdom. Language: English.. Summary Language: English.

AB The Third International Symposium on Immunotoxins was held on June 19-21, 1992 in Orlando, Florida. This symposium was sponsored by NATO, NIH, Pierce Chemical Company, Walt Disney Cancer Institute at Florida Hospital, Duke Comprehensive Cancer Center, Xoma, Immunogen, Seragen, Bristol-Myers Squibb, Chiron, Orth Biotech, Upjohn, Merck Sharp and Dohme Research Laboratories, Abbot Laboratories, Lilly Research Laboratories, and Evans and Sutherland. The Pierce Immunotoxin Award which recognizes outstanding contributions to immunotoxin research and development, was presented to Drs Dennis FitzGerald, Faith Wilson, David Eisenberg, and Ira Wool, for their contributions to the immunotoxin field.

L11 ANSWER 34 OF 33 SCISEARCH COPYRIGHT 2002 ISI (R)
93:43[illegible] The Genuine Article (R) Number: LL215. CONJUGATION OF APOLIPOPROTEIN-B WITH LIPOSOMES AND TARGETING TO CELLS IN CULTURE. LUNDBERG B (Reprint); HONG K; PAPAHADJOPOULOS D. ABO AKAD UNIV, DEPT BIOCHEM & PHARM, BOX 66, SF-20521 TURKU, FINLAND (Reprint); UNIV CALIF SAN FRANCISCO, CANC RES INST, SAN FRANCISCO, CA, 94143; UNIV CALIF SAN FRANCISCO, DEPT PHARMACOL, SAN FRANCISCO, CA, 94143. BIOCHIMICA ET BIOPHYSICA ACTA 24 JUL 1992 Vol. 1144, No. 2, pp. 305-312. ISSN: 0006-3002. Pub. Country: FINLAND; NVA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND TALL FORMATS

AB Mixed phospholipid cholesterol (1:1 molar ratio) liposomes were conjugated with native and acetylated apolipoprotein B (apoB), the **protein** part of low density lipoprotein (LDL). The objective was to increase the specificity of the cellular uptake of liposomes by utilization of the LDL and scavenger receptor pathways. The method of choice for the conjugation of liposomes with apoB proved to be the detergent solubilization and removal procedure. Two detergents were tested; sodium cholate (NaC) and octyl glucoside (OG). The integrity of the resulting complexes was demonstrated by Sepharose CL-4B gel chromatography and Metrizamide gradient centrifugation. The **conjugates** showed a good physical stability and the leakiness was only marginally larger than for unconjugated liposomes. The interaction of apoE- and acetyl apoB liposome **conjugates** with CV-1 and J774 cells, respectively, was monitored by an encapsulated pH-sensitive fluorophore, pyranine (8 hydroxy-1,3,6-pyrenetrisulfonate (HPTS)). This dye provides means of detecting binding and endocytosis of **conjugates** in living cells. The internalization was a fast process and about 10-times faster for the OG **conjugates** than for the corresponding unconjugated liposomes. The **conjugates** showed a clear concentration-dependent association of dye with cells, while this was less prominent with liposomes. The uptake was nearly an order of magnitude faster with CV-1 cells than with J774 cells. Acidification of **intracellular**

conjugates proceeded fast during the first 30 min of incubation and reached a minimum value of approx. pH 6 after 3 h. The specificity of binding of apoB-liposome **conjugates** to CV-1 cells was demonstrated by displacement experiments with native LDL. The results indicate that apoB-liposome **conjugates** may be used as a delivery vehicle for bioactive substances to cells.

L11 ANSWER 35 OF 39 CAPLUS COPYRIGHT 2002 ACS
1990:40018? Document No. 112:18? SV40 large T-antigen nuclear signal analogs: successful nuclear targeting with bovine serum albumin but not low molecular weight fluorescent **conjugates**. Lebl, Thomas J.; Mitchell, Mark A.; Maggiora, Linda L. (Upjohn Co., Kalamazoo, MI, 49001, USA). Biopolymers, 29(1), 19?-?03 (English) 1990. CODEN: BIPMAA. ISSN: 0006-3525.

AB The signal sequence of a nuclear-directed **protein** provides the necessary information for targeting the attached **proteins** to the cell nucleus. The sequence, structural requirements for a functional transport signal were explored with a series of peptides derived from the simian virus 40 large T-antigen nuclear signal 126-134 (CPPKKRKVED-NH2, wild type) conjugated to bovine serum albumin BSA through an N-terminal Tyr (Y) with m-maleimidobenzoyl-N-hydroxysuccinimide ester. Nuclear accumulation was virtually complete 15 min after microinjection into green monkey kidney cells TC-7. Peptides with Asn, Orn, and Gln substituted for Lys(14), the reverse wild-type peptide (DEVKRKKPC-NH2) and the long 24-residue wild-type analog (CYDDEATADQHSTPPKKSKTEDPKDPSEELL-NH2), were synthesized and conjugated similarly to BSA. The Orn peptide and the 24-residue wild-type analog conjugated to BSA also transported to the nucleus but at a slower rate than 1. The reverse wild-type, Asn-14 and Gln-BSA **conjugates** of these signal analogs did not show transport to the nucleus after 6 h of incubation. In an effort to learn if such signal sequences would also target a small mol. such as a fluorescent tag to the nucleus, 1 fluorescently tagged with monobromobimane was prepd. and microinjected into TC-7 cells. The peptide was distributed throughout the cell. These results support the notion that a pos. charged residue at position 14 is needed for rapid nuclear transport and that the **intracellular** transport machinery has spatial recognition. Results with fluorophore-peptide **conjugates** suggest nuclear localization of these low mol. wt. peptides will be difficult to attain even if attached to a functional nuclear localization sequence.

L11 ANSWER 34 OF 39 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
89213?84 EMBASE Document No.: 1989216684. Role of ligand in antibody-directed endocytosis of liposomes by human T-leukemia cells. Matthay K.K.; Abai A.M.; Gelb S.; Hong K.; Papahadjopoulos D.; Strandberger K.M.. Department of Pediatrics, University of California, San Francisco, CA 94143, United States. Cancer Research 49/17 4879-4?8? 1989. ISSN: 0008-5472. CODEN: CNREA8. Pub. Country: United States. Language: English. Summary Language: English.

AB The rate of uptake and **intracellular** processing of ligand-directed drug carriers may depend heavily on the endocytic pathway of the target antigen. We examined the role of the target antigen and type of antibody-liposome linkage in determining endocytosis of liposomes by three human T-cell leukemias, Jurkat, CEM, and Molt-4. Liposome-cell binding and internalization over time were studied using two independent assays for **intracellular** delivery of liposome contents: a new fluorescence assay using a pH-sensitive fluorescent dye; and a growth inhibition assay for delivery of cytotoxic drug, methotrexate-gamma-aspartate. Liposomes targeted against the transferrin receptor showed greater surface binding, internalization, and growth inhibition than liposomes targeted against the T-cell surface antigens, CD2, CD3, or CD5. Furthermore, liposomes made by conjugating the targeting antibody directly to the liposome surface were more efficiently internalized and retained

than were liposomes linked to antibody-coated cells via **Protein** A. Selection of the type of antibody-liposome **conjugate** as well as the appropriate surface receptor to facilitate endocytosis is essential in antibody-directed drug treatment of cancer.

L11 ANSWER 37 OF 39 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
89050065 EMBASE Document No.: 1989050065. Cytotoxic activity of daunorubicin or vindesin conjugated to a monoclonal antibody on cultured MCF-7 breast carcinoma cells. Abdul-Pirak E.; Leleur B.; Bhushana Rao K.S.P.; Baurain R.; Trouet A.; Schneider Y.-J.. Departement de Biochimie et de Biologie Cellulaire, Universite Catholique de Louvain, B 1340 Bruxelles, Belgium. Biochemical Pharmacology 38/4 641-648) 1989.
ISSN: 0006-2952. CODEN: BCPCA6. Pub. Country: United Kingdom. Language: English.. Summary Language: English.

AB **Conjugates** were constructed between daunorubicin or vindesin and a monoclonal antibody to human milk fat globule membrane associated antigen.. This antibody recognizes a high molecular weight glycoprotein present at the cell surface of human normal and tumour epithelial cells; after specific binding to plasma membrane of cultured MCF 7 human breast carcinoma cells, it is endocytosed and gains access to lysosomes, wherein it is broken down (Abdul-Pirak et al., Cancer Res 47: 1189-1196, 1988). Covalent linkage of daunorubicin (through a succinylated tetrapeptide arm) or of vindesin (through a hemisuccinate arm) yields **conjugates** with maximal molar ratios (drug molecule specific IgG under monomeric form, i.e. unaggregated) of 7.0 and 4.5 respectively. The **conjugate** with daunorubicin inhibits the binding of the ^{125}I labelled antibody to MCF-7 cells as efficiently as the native unconjugated antibody, whereas the **conjugate** with vindesin inhibits it only by 50%. Both **conjugates** are entirely stable in plasma and serum; after 24 hr incubation at pH 4.5 in the presence of rat liver lysosomal enzymes, 60% and 70% of daunorubicin and vindesin respectively are released from the **conjugates**. Adherent non-confluent cultures of cells recognized (MCF-7) or not (Hep-G2, human hepatocarcinoma cells) by the antibody were incubated from 2 hr to 6 days with different concentrations of daunorubicin or vindesin, free or conjugated to the specific or to a control monoclonal antibody. ID_{50}, defined as the drug concentration required to reach 50% of the amount of cell associated **protein** obtained in the absence of drug were determined at the end of 6 days continuous incubation or after shorter incubation followed by reincubation in drug free medium up to 6 days. Both cell lines are almost equally susceptible to the free drugs. The **conjugate** between daunorubicin and the antibody appears inactive, even at saturating concentrations of antibody. This could result from the extrusion out of the cells of daunorubicin molecules released from the **conjugate**, impairing the drug to reach the **intracellular** concentration required for cytotoxicity. In contrast, conjugation of vindesin to the specific but not to a control antibody restricts the activity of the drug to cells selectively recognized by the specific antibody. However, even after corrections for the loss of immunoreactivity and for the incomplete release of vindesin from the **conjugate**, cytotoxicity is achieved at higher concentrations or requires longer exposure to the conjugated than to the free drug. Nevertheless, these results clearly indicate that **drug targeting** relying on **conjugates** with monoclonal antibodies selectively recognized and endocytosed by target cells, covalently bound to a drug by a linkage stable in extracellular medium but hydrolysed within lysosomes, is valid. The pharmacological properties of the drug at the cellular level appear, however, to be also very important.

L11 ANSWER 38 OF 39 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
88141917 EMBASE Document No.: 1988141917. Binding and endocytosis of a monoclonal antibody to a high molecular weight human milk fat globule membrane-associated antigen by cultured MCF-7 breast carcinoma cells.

Abboud-Pirak E.; Sergent T.; Otte-Slachmuylder D.; Abarca J.; Trouet A.; Schneider Y.-J.. Universite Catholique de Louvain, Departement de Biochimie et de Biologie Cellulaire, B 1200 Bruxelles, Belgium. Cancer Research 48(11 (3184-3196) 1988.
ISSN: 0008-5472. CODEN: CNREA8. Pub. Country: United States. Language: English. Summary Language: English.

AB The aim of this study was to analyze whether a monoclonal antibody to human milk fat globule membrane-associated antigens, recognized specifically and homogeneously by human breast carcinoma cells but also by normal epithelial cells active in secretion, could be used to restrict the access of antitumoral drugs to cells exposing the epitope. The drug-antibody **conjugate** to be used is constructed by means of a covalent peptidic linkage stable in extracellular medium but hydrolyzed by lysosomal enzymes after endocytosis of the drug-carrier **conjugate**. This monoclonal antibody specifically immunoprecipitates radioactive material from MCF-7 cells biosynthetically radiolabeled with galactose, glucosamine, palmitic acid, or sialic acid but not with mannose, leucine, or methionine. Upon polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate and dithiothreitol, the label migrates as two bands with apparent molecular weights of about 350,000 and 400,000. These bands disappear, or their molecular weight is affected, after treatment of the cells with cycloheximide or of cell lysates with trypsin, Pronase, or neuraminidase but not treatment of the immunoprecipitate with endoglycosidase F. This suggests that these antigens are glycoproteins with O-linked oligosaccharides containing sialic acid in the epitope. By analogy, they should be similar, if not identical, to those recognized by the monoclonal antibodies designated HMFG1 (K. Burchell, H. Durkin, and J. Taylor-Papadimitriou, J. Immunol., 131: 508-513, 1983) and DF3 (K. Sekine, T. Ohno, and S.W. Kufe, J. Immunol., 139: 3610-3615, 1986). Binding at 4.degree.C of the 3H labeled antibody by MCF-7 cells indicates the specific attachment of about 1.2 x 10^6 IgG molecules per cells with a K(d) of about 14 nM. At 37.degree.C, cells take up the 3H-labeled antibody in amounts much higher than the binding capacity. In addition to cell-associated material, labeled digestion products are released into the culture medium. Cell fractionation by differential centrifugation and isopycnic equilibration on sucrose gradient indicates that the bulk of cell-associated antibody is distributed like the marker enzyme of lysosomes. Although the total uptake of the antibody by the cells is unaffected by either 50 .mu.M chloroquine or 5 .mu.g/ml cycloheximide, the release of digestion products is completely inhibited by chloroquine. Antigen-antibody dissociation is pH dependent, since, respectively, 50 and 84 of membrane-bound antibody are released during washing at pH 4.6 and 6.0. These results support the hypothesis that once bound to a plasma membrane epitope, the antibody is rapidly endocytosed and delivered to lysosomes for digestion. Antigen-antibody dissociation could occur as a result of a lower pH in endosomes and or lysosomes. Since the uptake at 37.degree.C far exceeds the 4.degree.C binding capacity of the plasma membrane and is continuous over extended periods of time, there must be a mechanism allowing the continuous supply of antigen to the plasma membrane. The absence of an effect of chloroquine, a drug known to increase the endosomal and lysosomal pH, on the uptake of the antibody suggests that dissociation of antibody from epitope at acid pH is not required for continuous supply to the plasma membrane. Since cycloheximide, a **protein** synthesis inhibitor, does not affect the uptake of the antibody, antigen neosynthesis does not seem to be involved. Therefore, the antigen could derive from a large **intracellular** pool, which is supported by binding of labeled antibody to cells preincubated with unlabeled antibody and then washed out in the presence of cycloheximide. All these results strongly suggest that this antibody is endocytosed, gains access to lysosomes, and could therefor be an appropriate carrier for **drug targeting** based on the lysosomotropic concept.

L11 ANSWER 39 OF 39 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
87089179 EMBASE Document No.: 1987089179. Anticancer agents coupled to N-(2-hydroxypropyl methacrylamide copolymers. I. Evaluation of daunomycin and puromycin **conjugates** in vitro. Duncan R.; Kopeckova-Rejmanova P.; Strohalm J.; et al.. Department of Biological Sciences, University of Keele, Keele, Staffordshire ST5 5BG, United Kingdom. British Journal of Cancer 55/2 (166-174) 1987. CODEN: BJCAAI. Pub. Country: United Kingdom. Language: English.

AB During recent years N-(2-hydroxypropyl methacrylamide (HPMA) copolymers have been developed as targetable drug carriers. These soluble synthetic polymers are internalized by cells by pinocytosis and they can be tailor-made to include peptidyl side-chains degradable intracellularly by specific lysosomal enzymes. Thus they provide the opportunity to achieve controlled **intracellular** delivery of anticancer agents. The anthracyclin antibiotic daunomycin, and **protein** synthesis inhibitor puromycin, were bound to HPMA copolymers via several different peptide side-chains, including Gly-Gly, Gly-Phe-Leu-Gly and Gly-Phe-Phe-Leu. Incubation of polymer-drug **conjugates** with isolated lysosomal enzymes (either a mixture of rat liver lysosomal enzymes or purified thiol-dependent lysosomal proteinases, cathepsins L and B) showed that significant release of drug occurred over 20 h, more than 20% of daunomycin and more than 3% of puromycin being liberated. To test their pharmacological activity **conjugates** were incubated with either the mouse leukemia L1210, or the human lymphoblastoid leukaemia CCRF in vitro. The **conjugates** tested were all less effective than free daunomycin, but they showed differential toxicity against L1210 depending on the aminoacid sequence of their drug-polymer linkage. Inclusion of thiopyridamine-terminating side-chains into the HPMA copolymer structure increased the affinity of **conjugates** for the L1210 cell membrane and resulted in increased toxicity. In contrast HPMA-daunomycin **conjugates** with or without thiopyridamine affected CCRF cell equally, but this cell line was more sensitive than the mouse leukemia to both free and polymer-bound daunomycin. Incubation of L1210 cells in polymer-bound daunomycin for 24 h, followed by plating cells out in low density in drug-free medium, showed that a concentration of polymer bound drug (1.64 .mu.g ml-1) could be selected to achieve a cytotoxic effect.

=> s estrogen conjugate
L12 791 ESTROGEN CONJUGATE

=> s l1 and bisphosphonate
L13 2 L1 AND BISPHOSPHONATE

=> dup remove l13
PROCESSING COMPLETED FOR L13
L14 2 DUP REMOVE L13 (0 DUPLICATES REMOVED)

=> d l14 1 2 cbib abs

L14 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
1992:630220 Document No. 117:230220 Treatment of osteoporosis with bisphosphonates and estrogens. Hooker, Jaclyn Elaine (Norwich Eaton Pharmaceuticals, Inc., USA). PCT Int. Appl. WO 9214474 A1 19920903, 40 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US864 19920131. PRIORITY: US 1991-661777 19910226.

AB Osteoporosis is treated in humans or animals with a bone-active phosphonate, esp. a **bisphosphonate** or a phosphonoalkylphosphonate [.gtoreq.0.1 LED (least ED)/day] and an estrogen

(.gtoreq.0.2-0.8 LED/day). Thus, a woman with postmenopausal osteoporosis was treated daily for 1 yr with 2-(3-pyridyl)-1-hydroxyethane-1,1-bisphosphonic acid (5 mg in a tablet) and 17.beta.-estradiol (0.03 mg from a transdermal patch).

L14 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
1993:66151 Document No. 118:66151 Conjugates for targeted delivery of bone growth factors. Bentz, Hanne; Rosen, David (Celtrix Pharmaceuticals, Inc., USA). Eur. Pat. Appl. EP 512844 A1 19921111, 9 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1992-304142 19920506. PRIORITY: US 1991-698467 19910510.

AB A bone growth factor, such as the transforming growth factor-.beta. (TGF-.beta.), activin and bone morphogenetic protein, are conjugated a targeting mol. with bone affinity (tetracycline, calcein, **bisphosphonate**, estrogen, etc.). Conjugation is carried out using a cross-linker, preferably a synthetic hydrophilic polymer, such as PEG. A soln. of 2 .mu.mol tetracycline in 1 .mu.mol bisepoxy-PEG was heated at 50.degree., followed by the addn. of a soln. of 100 .mu.g TGF-.beta. in 0.1% NaHCO3 borate reagent, 0.01% SDS and 10% acetonitrile and pH adjustment to 9, to give the TGF-.beta.-PEG-tetracycline conjugate.

=> s androgen conjugate
L15 52 ANDROGEN CONJUGATE

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16 34 DUP REMOVE L15 (18 DUPLICATES REMOVED)

=> d l16 1-34 abkt abs

L16 ANSWER 1 OF 34 CAPLUS COPYRIGHT 2002 ACS
2000:73922 Document No. 132:24475 A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women: effects on bone mineral density, symptoms and lipid profiles. Barrett-Connor, Elizabeth; Young, Ronald; Notelovitz, Morris; Sullivan, Jay; Wirta, Brinda; Wang, Hwa-Ming; Nolan, Joseph (Department of Family and Preventive Medicine, School of Medicine, University of California, San Diego, La Jolla, CA, 92093-0607, USA). Journal of Reproductive Medicine, 44(1), 1012-1100 English 1999. CODEN: JRPMAP. ISSN: 0024-7758. Publisher: Journal of Reproductive Medicine, Inc..

AB The effects of two doses of conjugated equine estrogen (CEE) and two of esterified estrogen plus methyltestosterone (E + A) were compared in surgically menopausal women. A two-year, parallel-group, double-blind study of 311 women who were randomly assigned to one of four regimens: (1) CEE, 0.625 mg/d; (2) CEE, 1.25 mg/d; (3) esterified estrogens, 0.625 mg, + methyltestosterone, 1.25 mg/d; or (4) esterified estrogens, 1.25, + methyltestosterone, 2.5 mg/d. Study parameters were symptoms, lipids, bone mineral d., side effects and safety. All treatments prevented loss of bone in the spine and hip. The higher E + A dose increased spine and hip BMD more than other treatments (P < 0.05). All treatments improved menopausal symptoms, with no significantly greater improvements in well-being and sexual interest in the E + A groups. Similar and significant decreases in low-d. lipoprotein were obsd. in all groups, but high-d. lipoprotein and triglycerides were increased only in the unopposed estrogen groups (P < 0.05). Hirsutism was uncommon and similar in all groups at two years. Discontinuation rates and reasons for withdrawal from the study were similar in both groups. No clin. significant side effects or lab. test abnormalities were seen. As compared to estrogen alone, E + A significantly improved BMD and was well tolerated in surgically menopausal women.

L16 ANSWER 2 OF 28 CAPLUS COPYRIGHT 2002 ACS
1998:527159 Document No. 129:170510 Rules for the design of the sequence and base composition of antisense oligonucleotides to maximize their effectiveness. Schlingensiepen, Karl-Hermann; Brysch, Wolfgang (Biognostik Gesellschaft fur Biomolekulare Diagnostik m.b.H., Germany). Eur. Pat. Appl. EP 854879 A2 19980805, 23 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI. (English). CODEN: EPXXDW. APPLICATION: EP 1997-101181 19970131.

AB Guidelines for the design of antisense oligonucleotides effective against a known gene are described. The complete sequence of the gene may be helpful in the design of antisense oligonucleotides. The antisense sequence has a length of 8-30 nucleotides. It contains no more than 6 bases or base analogs capable of forming three hydrogen bonds with cytosine. It does not contain four consecutive bases or base analogs capable of forming three hydrogen bonds with cytosine, i.e. the target sequence must not contain the sequence 5' CCC-3'. It also does not contain two sets of three consecutive bases or base analogs capable of forming three hydrogen bonds with cytosine, i.e. the target sequence must not contain two copies of the sequence 5' CCC-3'. The ratio between residues forming two hydrogen bonds per residue (X) with its target mol. and those residues forming three hydrogen bonds per residue (Y) must lie in the range 0.5 < X/Y < 2.

L16 ANSWER 3 OF 28 CAPLUS COPYRIGHT 2002 ACS
1998:92160 Document No. 128:75513 Novel steroid linked conjugates of 17.beta.-[N-[N'-(2-chloroethyl)-N'-nitrosocarbamoyl]amino acid and their antineoplastic activity against Noble Nb prostate carcinoma model in rats. Tang, W.; Schneider, M. R.; Eisenbrand, G. (Dep. of Chemistry, Division of Food Chemistry and Environmental Toxicology, University of Kaiserslautern, Kaiserslautern, 67653, Germany). Anti-Cancer Drug Design, 13(7), 815-824 (English) 1998. CODEN: ACDDEA. ISSN: 0266-9536. Publisher: Oxford University Press.

AB The novel steroid conjugates 17.beta.-[N-[N'-(2-chloroethyl)-N'-nitrosocarbamoyl]glycyl]-19-nortestosterone (1) and 17.beta.-[N-[N'-(2-chloroethyl)-N'-nitrosocarbamoyl]-L-alanyl]-19-nortestosterone (2) were synthesized and characterized with respect to affinity for steroid receptors and for androgenic efficacy. At an i.p. dosage of 50 mg/kg, conjugates 1 and 2 induced strong tumor inhibition of Nobel Nb prostate carcinoma in rats, but also a marked loss of body wt. In two further expts., treatment with conjugate 2 at a dose of 24 mg/kg demonstrated high antitumor activity without indication of toxicity. Conjugate 2 achieved the same tumor growth inhibition as a nearly twofold activity of 1 in the Noble Nb model at a well tolerated dosage. A low dose equimolar mixt. of unlinked N-(2-chloroethyl)-N-nitrosocarbamoyl-(CNC)-alanine and 19-nortestosterone was significantly more toxic than conjugate 2, showing about the same adverse effect on the body wt. as the conjugate at high dosage. CNC-L-alanine at equimolar dosage was highly toxic, causing early death of all animals.

L16 ANSWER 4 OF 28 CAPLUS COPYRIGHT 2002 ACS
1997:640578 Document No. 127:304518 Photodynamic therapy using nuclear hormone receptors to target photosensitizers. Mohr, Scott C.; Ray, Rahul (Trustees of Boston University, USA; Mohr, Scott C.; Ray, Rahul). PCT Int. Appl. WO 9734634 A2 19970925, 64 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US4542 19970321. PRIORITY: US 1996-13871 19960322.

AB The invention exploits a novel mechanism for photosensitizer localization,

namely interaction with the high-affinity receptors which mediate the hormonal signals transmitted by steroids (and some other hormones such as thyroxine, retinoids, and members of vitamin D family). These receptors are expressed only in specific cell types - and by their expression they confer hormone sensitivity on those cells. The invention provides hormone/chromophore conjugates which have reasonable binding affinity towards the hormone receptor protein and methods of administering them to patients as specific photosensitizing agents which can direct lethal damage towards receptor-pos. cell lines upon irradn. with visible light. These hormone/chromophore conjugates bound to nuclear hormone receptors can be used as selective mol. delivery systems for photodynamic therapy.

L16 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2003 ACS
1997:415594 Document No. 126:81102 Antisense oligonucleotides for prostate-specific antigen or probasin for chemotherapy of benign hyperplasia or cancer of the prostate. Tamesnik, Paul A. Worcester Foundation for Biomedical Research, USA; Tamesnik, Paul A. . PCT Int. Appl. WO 9711172 A1 19970327, 49 pp. DESIGNATED STATES: W: AU, CA, CN, JP, PL, RU, UZ; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US15123 19960920. PRIORITY: US 1995-4044 19950921.
AB Methods of selectively inhibiting the growth of or killing prostatic cells using antisense oligonucleotides to prostate-specific genes are disclosed. The oligonucleotides may have natural nucleic acid structures or may be modified oligonucleotides with enhanced stability or tissue specific targeting. The prostate specific genes to which the antisense may be directed include the PSA and the probasin genes. Pharmaceutical compns. including such antisense oligonucleotides are also described for use in the methods. The methods and products are of particular utility in the treatment of benign prostatic hyperplasia or prostate cancer.

L16 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2003 ACS
1997:350938 Document No. 126:81731 Antisense oligonucleotides to the androgen receptor and acidic fibroblast growth factor in chemotherapy of benign hyperplasia or prostate cancer. Tamesnik, Paul A. Worcester Foundation for Biomedical Research, USA; Tamesnik, Paul A. . PCT Int. Appl. WO 9711171 A1 19970327, 50 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, NZ, UZ; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US15081 19960920. PRIORITY: US 1995-4041 19950921.
AB Methods of selectively inhibiting the growth of or killing prostatic cells, using antisense oligonucleotides to prostate specific genes, are disclosed. The oligonucleotides may have natural nucleic acid structures or may be modified oligonucleotides with enhanced stability or tissue specific targeting. The prostate specific genes to which the antisense may be directed include the androgen receptor and acidic fibroblast growth factor genes. Pharmaceutical compns. including such antisense oligonucleotides are also described for use in the methods. The methods and products are of particular utility in the treatment of benign prostatic hyperplasia or prostate cancer.

L16 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2003 ACS
1997:51560 Document No. 127:90177 Marked decline in serum concentrations of adrenal C19 steroid precursors and conjugated androgen metabolites during aging. Labrie, Fernand; Belanger, Alain; Cusan, Lionel; Gomez, Jose-Luis; Candas, Bernard Laboratory Molecular Endocrinology, CHUL Res. Center, Le Centre Hospitalier Universitaire Quebec, Laval University, Quebec, G1V 4G2, Can.). Journal of Clinical Endocrinology and Metabolism, 82(8), 2396-2402 (English) 1997. CODEN: JCEMAG. ISSN: 0021-972X. Publisher: Endocrine Society.
AB The present data show a dramatic decline in the circulating levels of dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), androst-5-ene-3.beta.,17.beta.-diol (5-diol), 5-diol-sulfate, 5-diol-fatty acid esters,

and androstenedione in both men and women between the ages of 20-30 yr. In the 50- to 60-yr-old group, serum DHEA decreased by 74% and 70% from its peak values in 20- to 30-yr-old men and women, resp. The serum concns. of the conjugated metabolites of dihydrotestosterone (DHT), namely androsterone (ADT)-G, 5alpha.-androstane-3.alpha.,17.beta.-diol (5.alpha.-diol-G), androstane-3.beta.,17.beta.-diol (5.beta.-diol-G), and ADT-sulfate are the most reliable parameters of the total androgen pool in both men and women, whereas serum testosterone and DHT can be used as markers of testicular secretion in men and interstitial ovarian secretion in women. The serum concn. of these various conjugated androgen metabolites decreased by 40.8% to 72.9% between the 20- to 30-yr-old and 50- to 60-yr-old age groups in men and women, resp., thus suggesting a parallel decrease in the total androgen pool with age. As estd. by measurement of the circulating levels of these conjugated metabolites of DHT, it is noteworthy that women produce approx. 66% of the total androgens found in men. In women, most of these androgens originate from the transformation of DHEA and DHEA-S into testosterone and DHT in peripheral intracrine tissues, whereas in men the testes and DHEA and DHEA-S provide approx. equal amts. of androgens at the age of 50-60 yr. An addnl. potentially highly significant observation is that the majority of the marked decline in circulating adrenal C19 steroids and their resulting androgen metabolites takes place between the age groups of 20- to 30-yr olds and 50- to 60-yr-olds, with smaller changes are obsd. after the age of 60 yr.

L16 ANSWER 8 OF 36 MEDLINE DUPLICATE 1
97155142 Document Number: 97155142. PubMed ID: 9011956. Simplified profile of androgen glucuro- and sulfoconjugates in post-competition urine of sportsmen: a simple screening procedure using gas chromatography-mass spectrometry. Denenmin L; Laforge P; Dailly P; Bailloux D; Laforge J P. Laboratoire National de Depistage du Dopage, CREPS de Chatenay-Malabry, France.) JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL APPLICATIONS, (1996 Dec 6) 687 (1) 85-91. Journal code: 9417396. ISSN: 1378-4347. Pub. country: Netherlands. Language: English.

AB An analytical screening procedure has been developed for the estimation of total **androgen conjugates** in post-competition urine, using gas chromatography-mass spectrometry with computerized data acquisition and concentration calculation. Rapid acid-catalyzed methanolysis is a key feature of the method, which allows simultaneous cleavage of glucuronides and sulfates. Analytical data generated by this method for testosterone and epitestosterone are in accordance with our previous results obtained by more accurate isotope dilution mass spectrometry. The usefulness of the ratio of testosterone glucuronide/total epitestosterone as an aid for a better discrimination between physiologically high and pharmacologically high ratios of testosterone glucuronide/epitestosterone glucuronide, which was demonstrated previously, has been confirmed here.

L16 ANSWER 9 OF 36 MEDLINE DUPLICATE 2
96327334 Document Number: 96327334. PubMed ID: 8769403. [Clinical significance of testosterone and dihydrotestosterone metabolism in women]. Klinicko znacenje metabolizma testisterona i dihidrotestosterona u zena. Korsic M. (Zavod za endokrinologiju, dijabetes i bolesti metabolizma Klinike za unutarnje bolesti, KBC Sestre, Zagreb.) LIJECNICKI VJESNIK, (1996 Mar) 118 Suppl 1 , 1-6. Journal code: 0374233. ISSN: 0024-3477. Pub. country: Croatia. Language: Serbo-Croatian.

AB Hyperandrogenism in women refers to both excess androgen production and clinical manifestations of androgen excess. Clinical evaluation of women with hyperandrogenism is complex. The synthesis and release of androgenic steroid in women are normal part of adrenal and ovarian steroidogenesis. One of the classic questions concerning androgenic disorders concerns the source of circulating androgens. Relative roles of adrenal and ovary vary greatly, both can be involved. The use of gonadal or adrenal steroid administration can sometimes be used to distinguish the source of androgen

excess. In many cases of hyperandrogenism no laboratory diagnosis of adrenal and ovarian androgen overproduction can be made. These patients may have increased androgen sensitivity due to increased enzyme 5 alpha-reductase activity in the skin. To be active in the skin, testosterone (T) must be converted to dihydrotestosterone (DHT) by the 5 alpha-reductase. The increase in DHT production is a localized phenomenon and there is no generalized increase in enzyme activity in women with hyperandrogenism. DHT is rapidly converted to other steroid metabolites including androsterone, androstanediol and their glucuronide and sulfate conjugates. Although once thought to be specific for skin conversion of T to DTH these **androgen conjugates** reflect adrenal steroid production and metabolism. Antiandrogens (androgen receptor blockers) are the most effective therapeutic modalities of cutaneous hyperandrogenism. Clinical trials are in progress to determine efficacy of finasteride for the treatment of hirsutism and androgenetic alopecia. Finasteride is the first available medication of a new class of drugs that is an competitive inhibitor of 5 alpha-reductase and therefore should be beneficial for medical treatment of cutaneous hyperandrogenism.

L16 ANSWER 10 OF 16 MEDLINE DUPLICATE 8
95126173 Document Number: 95126173. PubMed ID: 7717633. Clinical relevance of testosterone and dihydrotestosterone metabolism in women. Rittmaster R. S. Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada. AMERICAN JOURNAL OF MEDICINE, (1995 Jan. 30) 98 (1A) 17S-21S. Ref: 31. Journal code: 1720. ISSN: 0002-9343. Pub. country: United States. Language: English.

AB Androgens are part of normal female physiology. When they are secreted in excess or when they cause unwanted symptoms such as hirsutism and male-pattern baldness, the term hyperandrogenism is used. In many hyperandrogenic women, there is no well-defined hormonal abnormality, but the women are simply on one end of a normal spectrum of androgen secretion and cutaneous androgen sensitivity. To be active in the skin, testosterone must be converted to dihydrotestosterone by the enzyme 5 alpha-reductase. Androgen sensitivity is determined, in part, by 5 alpha-reductase activity in the skin. This is a localized phenomenon, and there is no generalized increase in 5 alpha-reductase activity in these women. Dihydrotestosterone can be converted to glucuronide and sulfate conjugates, including androstanediol glucuronide. These **androgen conjugates** have been proposed to be serum markers of cutaneous androgen metabolism, but recent evidence indicates that they arise from adrenal precursors and are more likely to be markers of adrenal steroid production and metabolism. Antiandrogens (androgen receptor blockers) are the best medical treatment of cutaneous hyperandrogenism. 5 alpha-Reductase inhibitors have recently been approved for the treatment of benign prostatic hyperplasia, and research is currently underway to determine their effectiveness in treating hirsutism and male-pattern baldness.

L16 ANSWER 11 OF 16 CABA95 COPYRIGHT 2003 ACS
1995:416741 Document No. 122:184237 Clinical relevance of testosterone and dihydrotestosterone metabolism in women. Rittmaster, Roger S. (Camp Hill Medical Centre, Dalhousie University, Halifax, NS, Can.). American Journal of Medicine, 98 (1A), 17S-21S (English) 1995. CODEN: AJMEAZ. ISSN: 0002-9343.

AB A review, with 31 refs. Androgens are part of normal female physiol. When they are secreted in excess or when they cause unwanted symptoms such as hirsutism and male-pattern baldness, the term hyperandrogenism is used. In many hyperandrogenic women, there is no well-defined hormonal abnormality, but the women are simply on one end of a normal spectrum of androgen secretion and cutaneous androgen sensitivity. To be active in the skin, testosterone must be converted to dihydrotestosterone by the enzyme 5.alpha.-reductase. Androgen sensitivity is detd., in part, by 5.alpha.-reductase activity in the skin. This is a localized phenomenon, and there is no generalized increase in 5.alpha.-reductase activity in

these women. Dihydrotestosterone can be converted to glucuronide and sulfate conjugates, including androstanediol glucuronide. These **androgen conjugates** have been proposed to be serum markers of cutaneous androgen metab., but recent evidence indicates that they arise from adrenal precursors and are more likely to be markers of adrenal steroid prodn. and metab. Antiandrogens (androgen receptor blockers) are the best medical treatment of cutaneous hyperandrogenism. 5.alpha.-Reductase inhibitors have recently been approved for the treatment of benign prostatic hyperplasia, and research is currently underway to det. their effectiveness in treating hirsutism and male-pattern baldness.

L16 ANSWER 12 OF 34 CAPLUS COPYRIGHT 2001 ACS
1995:[illegible] Document No. [illegible]. Nucleic acid transfer peptides and their use for transfecting eukaryotic cells with nucleic acids. Brunner, Andre ; Darnhull, Jens; Moelling, Karin; Juni, Guenther-Gerhard (Boehringer Mannheim GmbH, Germany). PCT Int. Appl. WO 9420625 A1 19940915, 77 pp. DESIGNATED STATES: W: AU, CA, FI, HU, JP, KR, NO, NZ, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (German). CODEN: PIXXD2. APPLICATION: WO 1994-EP1147 19940409. PRIORITY: DE 1993-4307131 19930309; DE 1993-4314147 19930503.

AB A nucleic acid transfer peptide contains: a) a 1st ligand comprising a peptide, steroid, carbohydrate, lipid, or vitamin which binds to a binding partner at the surface of eukaryotic cells, triggering endocytosis of the complex composed of the nucleic acid transfer peptide and a nucleic acid; b) a 2nd ligand comprising a peptide, steroid, carbohydrate, lipid, or vitamin which binds to a binding partner on the outer membrane of the nucleus of eukaryotic cells; c) a 3rd ligand which is a basic peptide and binds to nucleic acids by ion exchange. These peptides are useful for: inserting nucleic acids into eukaryotic cells. Thus, the proliferation of Japan 1 human adenocarcinoma cells was inhibited by transformation with a mutant Ki-Ras ribozyme complexed with peptide AdSGD 1-35 (sequence given).

L16 ANSWER 13 OF 34 MEDLINE DUPLICATE 4
95010981 Document Number: 95010981. Pubmed ID: 7926[illegible]. Alterations in **androgen conjugate** levels in women and men with alopecia. Legro R S; Dunaif A; Kunselman A R; Demers L M; Strauss J F 3rd; Dodson W C; Lee P A. (Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles.) FERTILITY AND STERILITY, (1994 Oct) 62 (4) 744-51. Journal code: 0376727. ISSN: 0015-0282. Pub. country: United States. Language: English.

AB OBJECTIVE: To assess levels of androgen metabolites thought to reflect, at least in part, peripheral androgen activity in women with androgenic alopecia and men with premature balding in an effort to determine if a common abnormality exists. DESIGN: Prospective study in various groups of women and men. SETTING: Reproductive Endocrine Clinic at our university medical center. PATIENTS: Ten normal ovulatory female controls and 53 hyperandrogenic women divided on the basis of hirsutism and alopecia as follows: [1] 8 hirsute women with androgenic alopecia; [2] 12 nonhirsute women with androgenic alopecia; [3] 18 hirsute women without androgenic alopecia; and [4] 12 nonhirsute women without androgenic alopecia. Ten normal men and 11 young premature balding men matched for age and weight also were compared. INTERVENTION: Blood was obtained from all subjects. MAIN OUTCOME MEASURE: Comparison of blood hormone levels in the various groups. RESULTS: Serum T, androstenedione, and DHEAS were similarly elevated in hyperandrogenic women with and without alopecia, compared with controls. The female groups were then divided on the basis of hirsutism. Hirsute groups with and without alopecia had similarly elevated levels of unconjugated 3 alpha-androstanediol, 3 alpha-androstanediol glucuronide, 3 alpha-androstanediol sulfate, androsterone glucuronide, and androsterone sulfate compared with controls. In the nonhirsute groups, androgenic alopecia patients were compared with hyperandrogenic females and cycling controls. The androgenic alopecia patients had elevated levels of 3 alpha

androstanediol (0.75 +/- 0.11 versus 0.46 +/- 0.1 and 0.41 +/- 0.1 nmol/L), 3 alpha-androstanediol sulfate (200 +/- 31 versus 79.6 +/- 6 and 67.0 +/- 4.0 nmol/L), elevated ratios of 3 alpha-androstanediol sulfate:3 alpha-androstanediol (167 +/- 49 versus 170 +/- 20 and 164 +/- 49 nmol/L), elevated ratios of 3 alpha-androstanediol sulfate:3 alpha-androstanediol glucuronide (10.2 +/- [illegible] versus 1[illegible].[illegible] +/- 1 and 10.0 +/- 1) and lower ratios of 3 alpha-androstanediol glucuronide:3 alpha-androstanediol glucuronide (8.[illegible] +/- 1.[illegible] versus 17 +/- 1.7 and 1[illegible] +/- 1.6 nmol/L). In men the premature balding group had lower levels of 3 alpha-androstanediol glucuronide compared with the male controls (1[illegible].3 +/- 4.4 versus 15.2 +/- 1.6 nmol/L). Also, the ratio of 3 alpha-androstanediol glucuronide:3 alpha-androstanediol was significantly decreased, whereas the ratio of 3 alpha-androstanediol sulfate:3 alpha-androstanediol glucuronide was elevated. CONCLUSIONS: These data provides evidence confirming that enhanced 5 alpha-reductase activity occurs in androgenic alopecia but also suggests that a disorder of androgen conjugation, favoring sulfurylation over glucuronidation, may be a characteristic feature of scalp hair loss.

L16 ANSWER 14 OF [illegible] EMBASE COPYRIGHT 2[illegible] ELSEVIER SCI. B.V.
94321[illegible] EMBASE Document No.: 1[illegible]. Biochemistry of breast cyst fluid - I: Subgroups of breast cysts according to electrolytes, **androgen conjugate**, and epidermal growth factor levels. Enriori C.L.; Enriori P.J.; Harpe P.; Hirt J.; Lobenstein A.; Burell A.; Fritsches H.; Fischer J.F.; Engel H.; [illegible]; Lotteri M.G.; Morelli J.E.; Rebon P.; Hirsig R.J.F.; Etkin A.; [illegible]; Villamayor J.M.; Ruiz de Cornejo I.T.; Negri J.J.; et al.. Laboratorio de Analisis Clinicos,Cordoba 20[illegible], 1120-Buenos Aires, Argentina. Breast Disease 7/4 ([illegible]) 1994.
ISSN: [illegible]. CODEN: BRDIE[illegible]. Pub. Country: United States. Language: English. Summary Language: English.

AB Breast cyst disease, of unknown origin and spontaneously presenting cysts in the mammary gland, is a common problem in women, especially in the age range between [illegible] and 50. In the last decade, several studies have focused on the biochemical analysis of breast cyst fluids (BCFs). The present study assayed the intracystic Na+/K+ ratio (1[illegible] cysts) and the levels of dehydroepiandrosterone sulfate (DHEA-S, 195 cysts) and epidermal growth factor (EGF, 1[illegible]0 cysts). We found a significant inverse correlation between log Na+/K+ and log DHEA-S (r = -.7561; p <0.0001); log Na+/K+ and log EGF (r = -.[illegible]; p <0.0001); and a significant direct correlation between log DHEA-S and log EGF (r = +.[illegible]61; p <0.0001). The frequency polygons of DHEA-S and EGF levels appear to indicate a bimodal distribution with a cutoff of 7[illegible],000 ng/mL and [illegible] ng/mL, respectively, both arbitrarily chosen. In our series, 4[illegible].6% of BCFs present Na+/K+ .ltoreq. 3; [illegible] of DHEA-S .gtoreq. 7[illegible],000 ng/mL; and [illegible] of EGF levels .gtoreq. [illegible]50 ng/mL. However, only 11.[illegible]% of the cysts present Na+/K+ .ltoreq. 3 and simultaneously DHEA-S .gtoreq. 7[illegible],000 ng/mL and EGF .gtoreq. [illegible]50 ng/mL. These results may presumably have prognostic value that could be determined by a long-term follow-up of the patients.

L16 ANSWER 1[illegible] OF [illegible] EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 5
94122[illegible] EMBASE Document No.: 1[illegible]. **Androgen conjugates** as a measure of hyperandrogenism. Rittmaster R.S.. Gerard Hall, 13[illegible] Morris Street,Halifax, NS B3[illegible] 1B[illegible], Canada. Seminars in Reproductive Endocrinology 12/1 (45-[illegible]) 1994.
ISSN: [illegible]. CODEN: [illegible]RENE3. Pub. Country: United States. Language: English.

L16 ANSWER 1[illegible] OF [illegible] MEDLINE DUPLICATE 6
93259[illegible]87 Document Number: [illegible]. PubMed ID: 8491[illegible]51. **Androgen conjugates**: physiology and clinical significance. Rittmaster R S. (Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada. ENDOCRINE REVIEWS, (1993 Feb) 14 (1) 121-32. Ref: 95. Journal code: [illegible]006258. ISSN: 0163-769X. Pub. country: United States. Language: English.

L16 ANSWER 17 OF 38 CAPLUS COPYRIGHT 2002 ACS
1993:16978 Document No. 118:16978 Nonprotein intracellular hormone receptor binding conjugates and their use in diagnosis and therapy. Capelli, Christopher; Psaren, Herbert (USA). PCT Int. Appl. WO 9214493 A1 19920903, 19 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, MC, ML, MR, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US1107. 19920210. PRIORITY: US 1991-657772 19910220.

AB A targeting agent for the intracellular delivery of a therapeutic or diagnostic agent comprises a conjugate of (1) a nonprotein mol. which binds an intracellular hormone receptor; (2) a therapeutic or diagnostic agent; and (3) a linker moiety joining the agent to the nonprotein mol. The agents are useful for in vivo intracellular delivery of the therapeutic or diagnostic agent. 17.alpha.-Ethynylestradiol was conjugated to DTPA and then chelated with Gd to make a contrast agent for NMR imaging. In test mice, the signal intensity of uterine tissue was greater than that of the surrounding tissue.

L16 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2002 ACS
1993:94520 Document No. 118:94520 The ovarian contribution to peripherally derived serum C19 conjugates. Mattori, Robert P.; Stanczyk, Frank Z.; Cassidenti, Denise L.; Paulson, Richard J.; Lobo, Rogerio A. (Dep. Med., Univ. South. California, Los Angeles, CA, 90033, USA). Journal of Clinical Endocrinology and Metabolism, 1993, 76(1), 71-7 (English) 1992. CODEN: JCEMAZ. ISSN: 0021-972X.

AB While serum markers of peripheral androgen metab., such as 5.alpha.-androstane-3.alpha.,17.beta.-diol glucuronide (3.alpha.-diolG) and androsterone glucuronide (AnG), have been highly correlated with adrenal androgen prodn., the relative ovarian contribution to the pool of various C19 conjugates has not been fully investigated. The hypothesis was: whereas the ovary may not produce C19 conjugates directly, ovarian androgens, such as testosterone (T) and androstenedione (A), may be used as substrate for peripheral prodn. of these conjugates. To det. whether the ovary contributes directly to the pool of C19 conjugates, blood was obtained from the ovarian and peripheral veins of normal women (NW) at hysterectomy. To assess the indirect ovarian contribution to C19 conjugate prodn., the effect of ovarian suppression and stimulation on circulating 3.alpha.-diol and An conjugate levels was exam. in 10 NW and 11 anovulatory nonobese patients with polycystic ovary disease (NH-PCO). Ovarian suppression was carried out with leuprolide acetate (1 mg, s.c.) daily until the serum estradiol level was 30 pg/mL and was continued thereafter during ovarian stimulation with i.m. human menopausal gonadotropin or FSH. Blood samples were taken before, during, and after GnRH agonist suppression and just before hCG stimulation. Both unconjugated and conjugated androgens were quantified in serum by specific RIAs. No peripheral ovarian gradients were found for 3.alpha.-diol or An sulfates (3.alpha.-diolS or AnS) or glucuronides. In the NH-PCO group, both T and A levels were elevated, and they were suppressed to levels similar those in NW. With stimulation, T and A levels rose to higher levels than those had in NW. Both AnS and 3.alpha.-diolS, but not AnG and 3.alpha.-diolG, decreased with agonist suppression in the 2 groups; the decrease in levels of AnS and T correlated in the NH-PCO group. With stimulation, the An and 3.alpha.-diol conjugate levels increased in NH-PCO and were most marked for AnS and 3.alpha.-diolS, which were previously suppressed; the increase in AnG and A was correlated. While there is no evidence for the direct ovarian prodn. of C19 conjugates, these markers of peripheral androgen action are influenced by precursors from the ovary, principally A and T.

L16 ANSWER 19 OF 38 MEDLINE DUPLICATE 7
92288886 Document Number: 92288886. PubMed ID: 1600527. Using biological

measurements, can patients with benign breast disease who are at high risk for breast cancer be identified?. Miller W R; Scott W N; Harris W H; Wang D. Imperial Cancer Research Fund, Medical Oncology Unit, Western General Hospital, Edinburgh, Scotland.) CANCER DETECTION AND PREVENTION, (1992) 16 (4) 99-106. Journal code: 7704772. ISSN: 0361-090X. Pub. country: United States. Language: English.

AB In order to address the question of whether biological measurements might identify women with benign breast disease (BBD) at particular risk for breast cancer, analyses were performed on cyst fluids aspirated from patients presenting with palpable breast cysts. Electrolyte profiles showed that cyst fluids may be divided into major subpopulations which differ in terms of histological appearance of cyst lining epithelium, pattern of cyst presentation, and levels of other fluid constituents such as **androgen conjugates** and epidermal growth factor. Analysis of cyst fluids from 18 patients who subsequently developed breast cancer 1 to 5 years later showed that 12 individuals had group A cysts, three had group B cysts, and three presented with a mixture of the two types. Therefore, although this represents an increased proportion of group A cysts as compared with the total population of cyst fluids studied over the same time period, individuals subsequently developing breast cancer were not confined to one subgroup of cysts. **Androgen conjugate** and growth factor content also did not predict for subsequent cancer. At the present time, it is therefore concluded that biochemical measurements in cyst fluids cannot accurately identify women likely to develop breast cancer. However, the routine aspiration of cysts does provide the opportunity to monitor the local microenvironment of the breast.

L16 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2001 BIOLOGICAL ABSTRACTS INC.
1990:517749 Document No.: BA89:47297. BIOCHEMISTRY OF CYST FLUIDS AND ITS RELEVANCE. MILLER W.R. UNIV. DEP. CLINICAL ONCOLOGY, WESTERN GENERAL HOSP., EDINBURGH, UK.. CAPTABIETTA, L., ET AL. (ED.). ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, VOL. 595. STEROID FORMATION, DEGRADATION, AND ACTION IN PERIPHERAL TISSUES; FIRST INTERNATIONAL SYMPOSIUM, TAORMINA, ITALY, MARCH 14-16, 1989. XIII+488PP. NEW YORK ACADEMY OF SCIENCES: NEW YORK, NEW YORK, USA. ILLUS. (1990) [ ], 419-425. CODEN: ANYAA9. ISSN: 0077-8923. ISBN: 0-89766-[illegible]-X (PAPERB), 0-89766-565-1 (CLOTH). Language: English.

L16 ANSWER 11 OF 66 MEDLINE DUPLICATE 5
90219813 Document Number: 40 19813. PubMed ID: 2119213. Levels of **androgen conjugates** and oestrone sulphate in patients with breast cysts. Scott W N; Hawkins R A; Miller E; Miller W R. Department of Surgery, Royal Infirmary, Edinburgh, Scotland.) JOURNAL OF STEROID BIOCHEMISTRY, (1990 Dec) 35 (6) 823-6. Journal code: 0236125. ISSN: 0022-4731. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Plasma and cyst fluid were obtained from patients with palpable breast cysts and analysed for **androgen conjugates** and oestrone sulphate content by radioimmunoassay. Concentrations of **androgen conjugates** in cyst fluids varied from 19.6 to 477.5 mumols/l. These levels were much greater than those in plasma (1.3-5.1 mumol/l) and there was no association between values in cyst aspirates and plasma obtained from the same individuals. Levels of oestrone sulphate in breast cyst fluids (1.6-744.0 nmol/l) were also generally in excess of those in plasma (0.1-89.9 nmol/l) and again no relationship was evident between concentrations in cyst fluid and the circulation. Neither was there a relationship between levels of **androgen conjugate** and oestrone sulphate in plasma. In contrast, a highly significant correlation ($P less than 0.001) was identified between the **androgen conjugate** and oestrone sulphate content of cyst fluids. Levels of both **androgen conjugates** and oestrone sulphate were also significantly different in groups of cysts subdivided according to electrolyte classification,

cysts with low Na+:K+ ratios having higher steroid concentrations than those with high Na+:K+ ratios. The biological significance of the relationship between the two conjugates in cyst fluids remains unclear but it is suggested that the accumulation of these steroids involves a common mechanism.

L16 ANSWER 10 OF 18 MEDLINE DUPLICATE 7
90102617 Document Number: 90102617. Pubmed ID: 2332471. Androgen sulfate and glucuronide conjugates in nonhirsute and hirsute women with polycystic ovarian syndrome. Matteri R K; Stanczyk F Z; Gentzschein E E; Delgado C; Lobo R A. (Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles.) AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, (1989 Dec) 161 (6 Pt 1) 1704-9. Journal code: 0370476. ISSN: 0002-9378. Pub. country: United States. Language: English.

AB Peripheral androgen action largely determines the occurrence of hirsutism in women. Although serum 5 alpha-androstane-3 alpha, 17 beta-diol (5 alpha-diol) glucuronide signifies skin 5 alpha-reductase activity and has been used as a marker of hirsutism and peripheral androgen metabolism, other C19 **androgen conjugates** have recently been measured and may also be useful markers of hirsutism in women. In addition to normal controls we studied both hirsute and nonhirsute patients with polycystic ovarian syndrome who had similar levels of circulating androgen precursors. In these three groups we measured various C19 sulfates and glucuronides including serum 5 alpha-diol glucuronide. Serum androgen precursors were elevated, but were equal in the hirsute and nonhirsute patients. Serum androsterone sulfate and glucuronide, and 5 alpha-diol sulfate and glucuronide clearly differentiated the hirsute from the nonhirsute group. Among the conjugates, androsterone glucuronide was most reflective of the difference between the two groups (100.3 +/- 16.0 versus 41.9 +/- 4.8 ng/ml, p less than 0.05). In hirsute compared with nonhirsute patients with polycystic ovarian syndrome, serum 5 alpha-diol glucuronide was increased by the smallest amount (31%), followed by androsterone sulfate (38%), 5 alpha-diol sulfate (50%), and androsterone glucuronide with the largest increase (139%). Serum androsterone glucuronide and 5 alpha-diol glucuronide both correlated with androstenedione and dehydroepiandrosterone sulfate in hirsute women but not in nonhirsute women. These data suggest that besides serum 5 alpha-diol glucuronide, other C19 sulfate and glucuronide conjugates may reflect peripheral androgen action.

L16 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2008 ACS
1989:544915 Document No. 111:144909 A convenient, unified scheme for the differential extraction of conjugated and unconjugated serum C19 steroids on Sep Pak C18 cartridges. Payne, Donna W.; Holtorf, W. David; Adashi, Eli Y. Dep. Med., Univ. Maryland, Baltimore, MD, 21201, USA). Journal of Steroid Biochemistry, 33(1), 265-9 (English) 1989. CODEN: JSTBBK. ISSN: 0022-4731.

AB To conveniently and rapidly isolate by group both conjugated and unconjugated serum androgens, a scheme was devised for their differential extrn. in com. available, disposable octadecylsilane cartridges (Sep-Pak C18). Using added radioactive steroid stds. and detection of endogenous serum steroids by group-specific enzymic assays, the quant. recovery of steroid glucuronides and sulfates in the 47% MeOH fraction and of unconjugated steroids in the 100% MeOH fraction was used. Max. recovery of serum protein-bound steroids (e.g. testosterone) was achieved with serum denatured by urea and heat. To sep. glucuronides from sulfates, sequential hydrolysis of the conjugated fraction (47% MeOH) by enzymic hydrolysis and then dry. solvolysis as well as an addnl. Sep-Pak cartridge extrn. step was required. Groups of extd. steroids may be further sepd. and assayed by any appropriate method(s). An application is given which employs HPLC and an enzymic assay for 17.beta.-hydroxy- and 17-oxo-steroids to provide sep. profiles of unconjugated, glucuronidated, and sulfated androgens in human, male serum.

L16 ANSWER 24 OF 38 MEDLINE DUPLICATE 10
89380[illegible]09 Document Number: 89380009. PubMed ID: 2550402. Effect of MK-906, a specific 5 alpha-reductase inhibitor, on serum androgens and **androgen conjugates** in normal men. Rittmaster R S; Stoner E; Thompson D L; Hamon D; Lasseter K C. (Department of Medicine, Dalhousie University, Halifax, Nova Scotia.) JOURNAL OF ANDROLOGY, (1989 Jul-Aug) 10 (4) 259-62. Journal code: 8106492. ISSN: 0196-3635. Pub. country: United States. Language: English.

AB To determine the hormonal effects of MK-906, an orally active 5 alpha reductase inhibitor, on serum androgens and **androgen conjugates**, 11 healthy men were given 10, 100, 500, and 1000 mg MK-906 2 weeks apart in randomized order in a 4-period crossover design. Serum testosterone (T), dihydrotestosterone (DHT), androstanediol glucuronide, and androsterone glucuronide were measured before and 24 hours after each dose. The effect of MK-906 on glucuronyl transferase activity, the enzyme responsible for androstanediol glucuronide and androsterone glucuronide formation, was assessed in vitro using rat prostate tissue. Serum T levels were unchanged after all doses. Serum DHT, androstanediol glucuronide, and androsterone glucuronide were suppressed by 76%, 40%, and 5%, respectively, after the 10-mg dose, and by 84%, 72%, and 66% after the 1000-mg dose (P less than 0.05 for the comparison between the 10- and 1000-mg doses for all three steroids), respectively. Baseline serum T and DHT levels were strongly correlated ($R = 0.88$, $P = 0.0003$), as were androstanediol glucuronide and androsterone glucuronide levels ($R = 0.78$, $P = 0.003$), but there was no correlation between DHT levels and the levels of either conjugated steroid. MK-906 had no effect on glucuronyl transferase activity in vitro. It was concluded that single doses of MK-906 suppress both conjugated and unconjugated 5 alpha-reduced androgens. While all three steroids appeared to be good markers of systemic 5 alpha reductase inhibition, further research will be needed to determine which steroid best reflects tissue DHT levels in patients receiving these inhibitors.

L16 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2004 ACS
1989:111364 Document No. 111:111364 Reduction of reproductive losses by immunization of domestic animals with mixtures of steroid conjugates. Wilson, Patricia Ann; Cox, Ronald Ian; Wong, Michael Sai Pah; Paull, David Robert (Commonwealth Scientific and Industrial Research Organization, Australia). PCT Int. Appl. WO 8810078 A1 19881229, 50 pp. DESIGNATED STATES: W: AU, US; RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1987-AU204 19870710. PRIORITY: AU 1986-6055 19860711.

AB Losses of ova and embryos are reduced, and hence fecundity is increased, in sheep or other domesticated animals by actively immunizing the females against an androgen and an estrogen. Antibodies to these steroids are produced at levels which do not affect the display of behavioral estrus. The antibody levels decline by 50-90 percent during the mating period. Merino ewes were immunized s.c. with androstenedione-7.alpha.-carboxyethylthio ether (I) conjugated to human serum albumin [hapten d. (av. no. of steroid residues per amino acid residues) 3.7], testosterone-3-carboxymethyl oxime conjugated to bovine serum albumin (hapten d. 3.8), and 3 carboxymethylestrone conjugated to human serum albumin (hapten d. 3.4). The total nos. of ovulations (detd. by laparoscopy) and lambs born were 69 and 59, resp., in a group of 50 treated ewes, compared to 52 and 43, resp., in a similar group of controlled ewes. A booster immunization with the I conjugate alone the following year produced similar improvements in ovulation and lambing.

L16 ANSWER 26 OF 38 MEDLINE DUPLICATE 11
89002745 Document Number: 89002745. PubMed ID: 2971432. Epidermal growth factor in breast cyst fluid: relationship with intracystic cation and **androgen conjugate** content. Boccardo F; Valenti G;

Canardi G; Cerruti G; Fassio T; Bruzzi P; De Franchis V; Barreca A; Del Monte P; Minuto F. (Servizio di Oncologia Clinica, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.) CANCER RESEARCH, (1988 Oct 15) 48 (20) 5864-?. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB In recent years, several studies focused on the biochemical analysis of breast cyst fluid composition. It has been shown that breast cysts lined by apocrine epithelium contain higher levels of potassium and dehydroepiandrosterone-sulphate as compared to cysts lined by flattened cells, and that women with apocrine cysts are more likely to develop breast cancer. In the present study, we measured the intracystic levels of sodium (Na+), potassium (K+), dehydroepiandrosterone-sulphate (DHEA-S), and epidermal growth factor (EGF), a factor which could play a role in the autocrine- or paracrine control of breast cancer cell growth as recently proposed by some investigators. Breast cyst fluids obtained by fine-needle aspiration from 66 women with gross cystic breast disease were assayed. On the basis of the relative intracystic concentrations of Na+ and K+ two main classes of cysts were defined. An arbitrary cut-off value of 3 for the Na+/K+ ratio seemed adequate to separate these two types of cysts. An inverse relationship was found between the Na+/K+ ratio and DHEA-S concentration, median levels of the **androgen conjugate** being 6015 micrograms/l in Na+/K+ less than 3 cysts and 4.3 micrograms/l in Na+/K+ greater than 3 cysts ($P < 0.01$). EGF levels were found to be significantly higher in Na+/K+ less than 3 cysts as compared to Na+/K+ greater than 3 cysts: 109.26 ng/ml versus 57.22 ng/ml, respectively ($P < 0.001$). EGF appeared inversely correlated with total protein concentration in the Na+/K+ greater than 3 cysts, while in the Na+/K+ less than 3 cysts high EGF levels were observed independently of total protein content. In addition, a direct correlation was found between EGF and DHEA-S concentrations. On the basis of these results, the hypothesis can be made that EGF, which is measurable in all breast fluids tested and is nearly undetectable in plasma, is actually produced by the epithelium lining the cyst wall, particularly as far as the Na+/K+ less than 3 cysts are concerned. In view of our results this type of cyst, which has been shown to be lined by apocrine epithelium, appears to be characterized by high DHEA-S and EGF levels. It is suggested that the latter finding could provide a clue for understanding the increased risk of subsequent breast cancer in women bearing apocrine cysts.

L16 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2002 ACS

1987:413648 Document No. 107:18648 Steroid hormone conjugates for enhancing the fecundity of sows. Maclean, Colin William; Kilgariff, Michael John (Glaxo Group Ltd., UK). Fr. Demande FR 2572652 A1 19860509, 11 pp. (French). CODEN: FRXXBL. APPLICATION: FR 1984-16950 19841107. PRIORITY: GB 1984-28111 19841101.

AB The fecundity of sows, esp. of immature ones, is increased by immunization against one or more steroid androgens or estrogens, such as by administration of conjugates of these steroids with immunogenic supports. Thus, 7 mg 7.alpha.-[3-(4-carboxybutylthio)androst-4-ene]-3,17-dione in 5 mL dioxane was treated, at 10.degree., with 35 mg Et3N, followed by 28 mg iso-Bu chloroformate in 2.5 mL dioxane. After 40 min, the soln. was treated with 275 mg human serum albumin in 20 mL 0.1M phosphate buffer (pH 7.8) followed by dialysis and lyophilization. When administered together with DEAE-dextran adjuvant to 150-170-day-old sows, at 14-day intervals, the steroid-immunogen conjugate increases the no. of offspring per litter.

L16 ANSWER 28 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1987:75784 Document No.: BA84:35807. HORMONAL CORRELATES OF APOCRINE SECRETION IN THE BREAST. MILLER W R; DIXON J M; FORREST A P M. UNIV. DEP. CLIN. SURG., ROYAL INFIRMARY, EDINBURGH EH3 9YW, SCOTLAND. ANGELI, A., H. L. BRADLOW AND L. DOGLIOTTI (ED.). ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, VOL. 464. ENDOCRINOLOGY OF THE BREAST: BASIC AND CLINICAL

ASPECTS; INTERNATIONAL CONGRESS, TUPIN, ITALY, SEPT. 19-22, 1984. XVI+640P. THE NEW YORK ACADEMY OF SCIENCES: NEW YORK, N.Y., USA. ILLUS. (1986) 0 (0), 275-287. CODEN: ANYAA9. ISSN: 0077-8923. ISBN: 1-89766-323-3 (CLOTH), 0-89766-324-1 (PAPER). Language: English.

L16 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2002 ACS
1986:436949 Document No. 104:36949 Development of a gas chromatographic-mass spectrometric method using multiple analytes for the confirmatory analysis of anabolic steroids in horse urine. I. Detection of testosterone phenylpropionate administrations to equine male castrates. Dumasia, Minoo C.; Houghton, Edward; Finnie, Sharon (Racecourse Secur. Serv. Lab., Suffolk, CB8 7DT, UK). Journal of Chromatography, 377, 33-38 (English) 1986. CODEN: JOCRAM. ISSN: 0021-9673.

AB A gas chromatog.-mass spectrometric (GC-MS) method using 3 analytes to detect and confirm the administration to equine male castrates of veterinary prodrugs based on esters of testosterone is described. The method involves extn. of steroid conjugates from horse urine by C18-bonded cartridges and fractionation into glucuronic acid and sulfo-conjugates by Sephadex LH-20 column chromatog. After deconjugation, the free neutral steroids were partially purified by TLC and following derivatization (methyloxime-trimethylsilyl ether) were analyzed by capillary GC-MS in the selected-ion or full-scan mode. Of the 3 analytes, 5.alpha.-androstane-3.beta.,17.alpha.-diol could be detected in the glucuronic acid fraction for approx.10 days and 5.alpha.-androstane-3.beta.,17.beta.-diol and testosterone could be detected in the sulfo-conjugate fraction for 19 days after administration of a single therapeutic dose (50 mg. of Anabolject [1255-49-8]) to pure-bred and thoroughbred castrated male horses. The reasons for development of such a method, its validation and its potential for the detection of neutral metabolites of other veterinary anabolic steroids in horse urine are discussed.

L16 ANSWER 30 OF 38 MEDLINE DUPLICATE 12
85231149 Document Number: 85231149. PubMed ID: 3159597. An analysis of the content and morphology of human breast microcysts. Dixon J M; Scott W N; Miller W R. EUROPEAN JOURNAL OF SURGICAL ONCOLOGY, (1985 Jun) 11 (2) 151-4. Journal code: 8904854. ISSN: 0748-7983. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The composition of 41 human breast microcysts, dissected from eight biopsy and 14 mastectomy specimens has been analysed. All contained high concentrations of the **androgen conjugate**, dehydroepiandrosterone sulphate, the median value being more than 1000 times that of plasma. In ten cysts sufficient fluid was available for cationic analysis and in all the potassium concentration exceeded that of sodium. This composition suggests an apocrine derivation of the constituents of breast microcysts. This is substantiated by the finding of PAS diastase positive granules in the epithelium lining all 41 microcysts. These findings indicate that there is a single population of breast microcysts which are lined by epithelium with apocrine secretory activity.

L16 ANSWER 31 OF 38 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1984:80090 Document No.: BR26:80090. **ANDROGEN CONJUGATES** IN HUMAN BREAST SECRETIONS AND CYST FLUIDS. MILLER W R; FORREST A P M. UNIV. DEP. CLIN. SURG., MED. SCH., EDINBURGH EH8 9AG, SCOTLAND.. ANGELI, A., H. L. BRADLOW AND L. DOGLIOTTI (ED.). ENDOCRINOLOGY OF CYSTIC BREAST DISEASE. XVIII+325P. RAVEN PRESS: NEW YORK, N.Y., USA. ILLUS. (1983) 0 (0), 277-84. ISBN: 0-89004-866-2. Language: English.

L16 ANSWER 32 OF 38 MEDLINE DUPLICATE 13
84066149 Document Number: 84 66149. PubMed ID: 6645454. Formation of **androgen conjugates** by porcine granulosa cells.
Lischinsky A; Khalil M W; Hobkirk R; Armstrong D T. JOURNAL OF STEROID BIOCHEMISTRY, (1983 Oct) 19 (4) 1435-40. Journal code: 0260125. ISSN: 0022-4731. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The relative abilities of isolated and recombined theca and granulosa cells, derived from medium-sized porcine ovarian follicles, to synthesize androgens and estrogens were compared. Isolated thecal preparations produced large amounts of immunoreactive androstenedione and testosterone. When theca was co-cultured with granulosa cells, accumulation of both these androgens was markedly less. Though the co-cultures produced significantly higher amounts of estradiol, this increase did not account for the reduced androgen production. To determine if the lesser androgen accumulation in the combined cultures was due to metabolism by granulosa cells of androgens to other metabolites, the fate of [3H]androstenedione or [3H]testosterone was followed. Whenever granulosa cells were present in the incubation dishes, most of the radioactivity remained in the aqueous fraction after ether extraction. Examination of the aqueous fraction by DEAE-Sephadex A25 demonstrated the presence of androgen sulphates. The results suggest that granulosa cells are the site at which follicular formation of androgen sulphates takes place.

L16 ANSWER 33 OF 38 MEDLINE DUPLICATE 14
84002394 Document Number: 84002394. PubMed ID: 6225560. Classification of human breast cysts according to electrolyte and **androgen conjugate** composition. Miller W R; Dixon J M; Scott W N; Forrest A P. CLINICAL ONCOLOGY, 1983 Sep; 9 (3): 327-31. Journal code: 7511426. ISSN: 0305-7232. Pub. country: ENGLAND: United Kingdom. Language: English.
AB One hundred human breast cyst fluids have been analysed for sodium (Na+), potassium (K+) and dehydroepiandrosterone (DHA) sulphate. Concentrations varied greatly between individual cyst fluids, Na+ from 2 to 135 mmol/l, K+ from 5 to 76 mmol/l and DHA-sulphate from 1.5 to 77 mumol/l. Analysis of the inter-relationships between Na+, K+ and DHA sulphate revealed two major sub-populations of cyst fluids--one group in which Na+ levels were markedly in excess of K+ and DHA sulphate concentrations were low and the other in which K+ was the predominant cation and DHA sulphate concentrations were high.

L16 ANSWER 34 OF 38 MEDLINE DUPLICATE 15
83034554 Document Number: 83034554. PubMed ID: 6185501. **Androgen conjugates** in human breast cyst fluids. Miller W R; Roberts M M; Creel R J; Wang D Y; Reilly R W; Forrest A P. JOURNAL OF THE NATIONAL CANCER INSTITUTE, 1982 Nov; 69 (5): 1059-8. Journal code: 7510795. ISSN: 0027-8874. Pub. country: United States. Language: English.
AB Dehydroepiandrosterone sulfate (DHAS) has been measured by radioimmunoassay in 100 breast cyst fluids obtained from 42 women. Values ranged from 1.5 to 1,111 micromM with a median of 140 micro M. These concentrations are in excess of those for plasma but are comparable or less than values for breast secretions obtained by nipple aspiration. Levels of DHAS in cyst fluid were not significantly affected by age, menopausal status, or parity of the subject or by the volume of cyst fluid obtained. In patients with multiple cysts, DHAS values from cysts aspirated from the same breast on the same date were relatively comparable, but wide variations were frequently observed between cysts aspirated on different occasions from the same breast and between cysts from different breasts of the same patient, whether samples simultaneously or sequentially. Such variability must complicate comparative studies among women.

L16 ANSWER 35 OF 38 MEDLINE DUPLICATE 16
76246476 Document Number: 76246476. PubMed ID: 941181. Androgen metabolism by rat epididymis. 4. The formation of conjugates. Djoseland O. STEROIDS, (1976 May) 27 (5) 617-26. Journal code: 0404536. ISSN: 0039-128X. Pub. country: United States. Language: English.
AB The ability to form **androgen conjugates** and the hormone dependency of the conjugating enzymes have been studied in the rat epididymis. Following the in vitro incubation of 3H-testosterone with epididymal slices from intact and castrated rats, the radioactivity

recovered was partitioned between water and ether. Examination of the water soluble radioactivity demonstrated the presence of glucuronides and sulfates. The total radioactivity in the conjugate fraction was the same for both intact and castrated animals. However, castrated rats showed a 3-fold increase in the glucuronide fraction with a corresponding decrease in the formation of sulfates. Characterization of the ether soluble radioactivity after solvolysis of the conjugate fraction from castrated animals, showed DHT (17beta-hydroxy-5alpha-androstan-3-one) and 5alpha-diol (5alpha-androstane-3alpha, 17beta-diol) to be the main metabolites. After beta-glucuronidase hydrolysis of the same, only 5alpha-diol could be demonstrated at a significant level, although traces of DHT and delta5 compounds were present. Corresponding hydrolysis of the water phase from incubation of epididymis from intact rats, demonstrated a marked quantitative difference. Here approximately 4[illegible] of the conjugated aglycones consisted of delta5 compounds, whilst only about 12% was comprised of 5alpha-diol. The preferential conjugation of DHT and 5alpha-diol to a sulfate radical was demonstrated in both intact and castrated rats. Since the conjugated delta5 compounds were detected only in the epididymis from intact animals, it is possible that these are formed by the spermatozoa.

L16 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2002 ACS
1972:443488 Document No. 77:43488 Metabolism of testosterone N-acetylglucosaminide. Fukushima, David K.; Matsui, Michio; Bradlow, H. L.; Hellman, Leon (Inst. Steroid Res., Montefiore Hosp. Med. Cent., New York, N. Y., USA.). Steroids, 19(3), 335-43. English. 1972. CODEN: STERAM.

AB Following i.v. administration of 4-14C-labeled testosterone 17-N-acetylglucosaminide (I) [21153-51-0] to a human, urinary excretion of radioactivity was rapid. The administered steroid aminosugar conjugate was the predominant radioactive compd., and etiocholanolone and androsterone conjugated with glucuronic acid were present in a ratio of approx. 7:1. Following oral I, only traces of testosterone conjugated with the aminosugar were found; etiocholanolone and androsterone again occurred in a 7:1 ratio. Metabolism of the labeled glucosaminide revealed that: 1) cleavage of the glycosidic linkage was almost complete by the oral route, 2) cleavage of the glycosidic group occurred subsequent to redn. of the A ring since the metabolic pattern of the testosterone conjugate differed from that of testosterone ingested by the same subject, and (3) there was a directive influence of the aminosugar toward 5.beta.-redn. favoring etiocholanolone over androsterone.

L16 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2002 ACS
1971:471412 Document No. 75:71412 Metabolism of steroid conjugates. VI. In vivo perfusion of the human liver with synthetic 7.alpha.-3H-dehydroepiandrosterone sulfatide. (Bertel, H. W.; Mappes, G.; Wortmann, W. Abt. Exp. Endokrinol., Univ. Frankfurt, Mainz, Ger.). Horm. Metab. Res., 3(4), 244-6 (English) 1971. CODEN: HOMHAZ.

GI For diagram(s), see printed CA Issue.

AB Following in vivo perfusion of human liver with tritiated dehydroepiandrosterone sulfatide (I.sulfatide), 1.1[illegible]2% of the 3H-activity was demonstrated in hepatic venous blood in the free steroid and steroid glucuronide fractions. I metabolites in these various fractions accounted for 4[illegible] of the isolated 3H-activity. Androst-5-ene-3.beta.,17.beta.-diol, 16.alpha.-hydroxydehydroepiandrosterone, androst-5-ene-3.beta.,7.alpha.,17.beta.-triol, androsterone, and etiocholanolone were the major I metabolites found. In general, the hydrolysis and metabolism of I.sulfatide greatly exceeded that found after perfusion of human liver with I.sulfate.

L16 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2002 ACS
1969:93529 Document No. 70:93529 Extraction of steroid conjugates from aqueous solutions. Kammer, Charles S.; Goldzieher, Joseph W. (Div. of

Clin. Sci., Southwest Found. for Res. and Educ., San Antonio, Tex., USA). Anal. Biochem., 28(1-3), 492-512 English) 1969. CODEN: ANBCA2.

AB The extn. of radioactive steroid conjugates from 0.3M pyridinium sulfate in water or urine by various solvents was studied quant. The pure conjugates exam'd. included the sulfates of dehydroepiandrosterone, testosterone, and estrone, and the glucuronides of dehydroepiandrosterone and testosterone. Biol. conjugate mixts. were prepd. by injection of progesterone, estradiol, hydrocortisone, and 11.beta.-hydroxyandrost-4-ene-3,17-dione into humans, rabbits, or baboons, and collection of urine. Extn. of the pyridinium sulfate soln. with CHCl3-EtOAc (1:1) was efficient for the pure model conjugates tested. The more complex biol. conjugate mixts. were best extd. with CHCl3-tert-BuOH 5:1), except for the hydrocortisone metabolites, which required CHCl3-BuOH (4:1). The extns. were appreciably cleaner than those obtained with the widely used BuOH-EtOH procedure.

=> s FKBP conjugate
L17 1 FKBP CONJUGATE

=> d l17 ckib abs

L17 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
1994:412794 Document No. 121:212794 Conformational Changes of Rapamycin and Analogs upon Complexing with FKBP Associated with Activity: An Application of Second Derivative CD Spectroscopy. Chen, Yanqiu; Zhou, Peng; Borova, Nina; Zhang, Huaizhi; Nakanishi, Koji; Bailli, Amedeo; Steffan, Robert J.; Molnar-Kimber, Katherine; Caggiano, Thomas J. (Department of Chemistry, Columbia University, New York, NY, 10027, USA). Journal of the American Chemical Society, 116(6), 2283-4 (English) 1994. CODEN: JACSAT. ISSN: 0002-7863.

AB The CD spectra of **FKBP conjugates** of rapamycin and some of its analogs are reported. The neg. Cotton effect at 210 nm is enhanced in the conjugates and the Cotton effect of the triene absorption at approx.279 nm shows both enhanced vibrational structure and a sign inversion. The latter trend is clearer in the second deriv. CD and indicates that the triene moiety in the conjugates adopts a more rigid and planar conformation. The sign inversion of the Cotton effect reflects the chiral influence of the FKBP binding site. The CD curves of mixts. of FKBP with allylated or lysine-substituted rapamycin are superimposable on the summation CD curves of the free drug and FKBP.

=> s Hsp70 conjugate
L18 1 HSP70 CONJUGATE

=> d l18 ckib abs

L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
1998:186183 Document No. 128:240181 Vaccines for inducing cell-mediated cytolytic response comprising antigen and stress protein. Mizzen, Lee; Anthony, Lawrence S. J. (Stressgen Biotechnologies Corp., Can.; Mizzen, Lee; Anthony, Lawrence S. J.). PCT Int. Appl. WO 9813373 A1 19980604, 71 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-CA897 19971125. PRIORITY: US 1996-756621 19961126.

AB The present invention relates to a vaccine for inducing an immune response to an antigen in a vertebrate (e.g., mammal) comprising an antigen and all

or a portion of a stress protein or all or a portion of a protein having an amino acid sequence sufficiently homologous to the amino acid sequence of the stress protein to induce the immune response against the antigen. In a particular embodiment, the present invention relates to vaccines and compns. which induce a CTL response in a mammal comprising an antigen and all or a portion of a stress protein. In another embodiment, the invention relates to vaccines and compns. which induce an immune response to an influenza virus in a mammal comprising an antigen of the influenza virus and all or a portion of one or more stress proteins. The invention also relates to vaccines and compns. for inducing a CTL response to a tumor-assocd. antigen comprising a tumor-assocd. antigen and all or a portion of the stress protein. The invention also relates to vaccines and compns. for suppressing allergic immune responses to allergens comprising an allergen and all or a portion of a stress protein. Immunogens comprising influenza virus NP peptide and Mycobacterium hsp70, NP peptide-**hsp70 conjugates** and NP peptide-hsp70 fusion proteins were prepd. Mice immunized with these preps. displayed a CTL response against cells exhibiting the NP peptide.

=> s rapamycin conjugate
L19 7 RAPAMYCIN CONJUGATE

=> dup remove l19
PROCESSING COMPLETED FOR L19
L20 7 DUP REMOVE L19 (0 DUPLICATES REMOVED)

=> d l20 1-7 abib abs

L20 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:112769 Document No.: PREV200200112769. Rapamycin position 27 conjugates. Millar-Kimber, Katherine L. [1]; Chatfield, Craig E.; Cobain, Timothy J.; Farrell, Amadeo A. [1] Worcester, IA USA. ASSIGNEE: American Home Products Corporation. Patent Info.: US 6211176 December 11, 2001. Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 11, 2001) Vol. 1255, No. 2, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133. Language: English.

Ab Provided are **rapamycin conjugates** which are useful as immunogenic molecules for the generation of antibodies specific for rapamycin or a derivative thereof, for measuring levels of rapamycin or derivatives thereof; for isolating rapamycin binding proteins; and detecting antibodies specific for rapamycin or derivative thereof. This invention also provides monoclonal antibodies specific for rapamycin or a ring opened derivative of rapamycin.

L20 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
2000:168500 Document No. 132:171073 Conjugates targeted to target receptors and/or interleukin-2 receptors. Prakash, Haresh K.; Clemons, Christopher M. Watson Laboratories, Inc.-Utah, USA). PCT Int. Appl. WO 2000007643 A2 20000217, 67 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE, BN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US17043 19990804. PRIORITY: US 1998-128572 19980804.

AB A compn. for intracellular delivery of a chem. agent into a target receptor and/or interleukin-2-receptor-bearing cell, e.g. an activated T cell and cancer cell, includes a chem. agent, at least one copy of target-receptor binding and/or an interleukin-2-receptor-binding and endocytosis-inducing ligand coupled to a water sol. polymer. The ligand

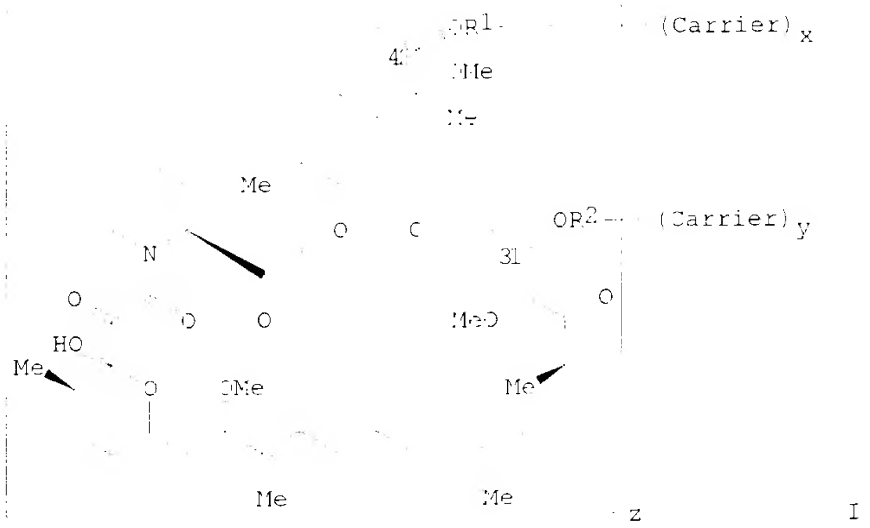
binds to a target receptor and/or IL-2 receptor on the target receptor and/or IL-2-receptor-bearing cell and elicits endocytosis of the compn. The compn. also optionally includes a biodegradable spacer for coupling the chem. agent and the ligand to the polymer. Chem. agents can include cytotoxins, transforming nucleic acids, gene regulators, labels, antigens, drugs, and the like. A preferred water sol. polymer is polyalkylene oxide, such as polyethylene glycol and polyethylene oxide, and activated derivs. thereof. The compn. can further comprise a carrier such as another water sol. polymer, liposome, or particulate. Methods of using these compns. for delivering a chem. agent in vivo or in vitro are also disclosed. A method of detecting a disease, such as cancer, T-cell lymphocytic leukemia, T-cell acute lymphoblastic leukemia, peripheral T-cell lymphoma, Hodgkin's disease, and non-Hodgkin's lymphoma, assocd. with elevated levels of soluble target receptor and/or IL-2 receptor is also disclosed.

L20 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2000 ACS
1998:6824[illegible] Document No. 128:3149[illegible] Method for production of antibodies to specific sites of rapamycin. Watanabe, Randall W.; Malcolm, Andrew J.; Natchev, Peltcharp (Isotechnika, Inc., Can.). PCT Int. Appl. WO 9845333 A1 19981015, 38 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, DE, DK, EA, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US6369 19980409. PRIORITY: US 1997-41214 19970409.

AB This invention relates to the prodn. of polyclonal and monoclonal antibodies to specific sites of rapamycin (sirolimus). The reactivity of these polyclonal and monoclonal antibodies make them particularly useful for immunoassays for therapeutic drug monitoring (TDM). **Rapamycin conjugate** immunogens are prepd. for the immunization of a host animal to produce antibodies directed against specific regions of the rapamycin mol. By detg. the specific binding region of particular antibody, immunoassays which are capable of distinguishing between the parent mol., active metabolites, inactive metabolites and related mols. are developed. The use of divinyl sulfone (DVS) as the linker arm mol. for forming rapamycin-protein conjugate immunogens is described. DVS-linked rapamycin-protein conjugates were found to elicit antibodies with greater specificity to the rapamycin mol. than glutaric linked conjugates.

L20 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2000 ACS
1995:452[illegible] Document No. 122:21885[illegible] Preparation of **rapamycin conjugates** for generation of antibodies. Milnar Kimber, Katherine Lu; Cobain, Timothy Donald; Caulfield, Craig Eugene; Caggiano, Thomas Joseph; Failli, Amedeo Arturo (American Home Products Corp., USA). PCT Int. Appl. WO 9405071 A1 19941110, 41 pp. DESIGNATED STATES: W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LT, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US4463 19940422. PRIORITY: US 1993-53031 19930423; US 1994-224207 19940414.

GI



AB Title compds. I [(R1, R2 = H, (R3LR4) wherein L = linking group, R3 = CO, SO, SO2, PO2, POMe, CS, CH2O; R4 = O, NH, S, CH2, O; a = 1-5; z = 1-120), carrier = immunogenic material, detector material, solid matrix, salt; x, y = 0,1 with provisos], are prepd. Succinic anhydride and dimethylaminopyridine were added to II to give II 42-ester with succinic acid which was treated with N-hydroxysuccinimide to give II 42-ester with N-hydroxysuccinimide hemisuccinate which was conjugated with proteins and horseradish peroxidase. Screening for monoclonal antibodies specific for II or its derivs. as well as immunoassay are given.

L20 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
1995:214217 Document No. 122:52081 **Rapamycin conjugates** and antibodies. Gonzalez, Eduardo; Russell, John C.; McGnar-Kimber, Katherine L. (Abbott Laboratories, USA). PCT Int. Appl. WO 9425482 A1 19941110, 38 pp. DESIGNATED STATES: W: AU, CA, JP, KR; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US4434 19940422. PRIORITY: US 1993-53030 19930423; US 1994-224109 19940414.

AB An immunoassay method for detn. of rapamycin in blood comprises the use of rapamycin or secorapamycin 42-ester conjugates with fluorescein derivs. as immunogenic mols. for the generation of antibodies specific for rapamycin. Rapamycin 42-ester with succinic acid (100 mg) reacted overnight with 12 mg of N-hydroxysuccinimide to obtain rapamycin 42-ester with N-hydroxysuccinimide hemisuccinate (I). To 4.2 mg of 5-glycinylfluoresceinamide, 4 mg of I was added and after reaction for 2 h the conjugate obtained was purified by TLC.

L20 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
1995:243941 Document No. 122:54000 Monoclonal antibody to rapamycin for immunoassay. Quesniaux, Valerie; Sedrani, Richard (Sandoz-Erfindungen Verwaltungsgesellschaft mbH, Austria; Sandoz-Patent-G.m.b.H.; Sandoz Ltd.). PCT Int. Appl. WO 9424304 A1 19941027, 35 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KE, KG, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, US, UZ, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1994-EP1006 19940330. PRIORITY: GB 1993-7491 19930408.

AB Monoclonal antibodies to rapamycin and to 40-O-alkylated derivs. of rapamycin are provided, together with nobel haptens, immunogenic conjugates, and processes for making them and assay kits for using them.

In example, 40-O- and 28-O-activated rapamycin derivs. and their immunogenic conjugates with keyhole limpet hemocyanin or ovalbumin or albumin were prepd. for monoclonal antibody prodn. for use in ELISA of rapamycin.

L 0 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS
1994:432799 Document No. 121:32799 Conformational Changes of Rapamycin and Analogs upon Complexing with FKBP Associated with Activity: An Application of Second Derivative CD Spectroscopy. Chen, Yanqiu; Zhou, Peng; Berova, Nina; Zhang, Hongzhi; Nakanishi, Koji; Failli, Amedeo; Steffan, Robert J.; Molnar-Kimber, Katherine; Caggiano, Thomas J. (Department of Chemistry, Columbia University, New York, NY, 10027, USA). Journal of the American Chemical Society, 116(6), 2653-4 (English) 1994. CODEN: JACSAT. ISSN: 0002-7863.

AB The CD spectra of FKBP conjugates of rapamycin and some of its analogs are reported. The neg. Cotton effect at 210 nm is enhanced in the conjugates and the Cotton effect of the triene absorption at approx.270 nm shows both enhanced vibrational structure and a sign inversion. The latter trend is clearer in the second derivs. CD and indicates that the triene moiety in the conjugates adopts a more rigid and planar conformation. The sign inversion of the Cotton effect reflects the chiral influence of the FKBP binding site. The CD curves of mixts. of FKBP with silylated or lysine-substituted rapamycin are superimposable on the summation CD curves of the free drug and FKBP.

=> s geldanamycin conjugate
L1 0 GELDANAMYCIN CONJUGATE

=> s tacrolimus conjugate
L2 1 TACROLIMUS CONJUGATE

=> d l2 cbib abs

L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:131194 Document No. 134:146894 Immunoassay of tacrolimus with monoclonal antibody having reduced cross-reactivity with tacrolimus metabolites. Kasper, Kenneth C.; Jeang, Henry; Davalian, Darioush; Liu, Hshiou-ting; Miller, Paul L.; Williams, Denise L. (Dade Behring Inc., USA). PCT Int. Appl. WO 2001009190 A2 20010208, 60 pp. DESIGNATED STATES: W: AU, CA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US21186 20000803. PRIORITY: US 1999-368018 19990803.

Ab An IgG1 monoclonal antibody to the immunosuppressive drug tacrolimus has improved properties. In particular, this monoclonal antibody, designated 3E8, has reduced cross reactivity to several tacrolimus metabolites. This antibody is suitable for performance of immunoassays such as homogeneous immunoassays to detect or det. the presence or concn. of tacrolimus in samples such as blood samples. The invention further includes derivs. of tacrolimus derivatized at a non-binding portion of the mol. useful in immunizing antibody-producing animals and in producing such monoclonal antibodies, as well as labeled derivs. of tacrolimus useful as tacrolimus analogs in such assays. The invention further includes immunoassay methods for the detection of tacrolimus and test kits useful in performing such immunoassays.

=> d FKBP conjugate
'FKBP' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'
'CONJUGATE' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

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ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
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DMAX -------- MAX, delimited for post-processing
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FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
              SCAN must be entered on the same line as the DISPLAY,
              e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

TABS -------- ABS, indented with text labels
TALL -------- ALL, indented with text labels
TBIB -------- BIB, indented with text labels
TMAX -------- MAX, indented with text labels
TTD --------- TTD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OTBIB ------- OBIB, indented with text labels

ZBIB -------- BIB, no citations
ZTBIB ------- TBIB, no citations

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              containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

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FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC
to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):bib

L22  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
AN   2001:101194  CAPLUS
DN   134:146399
TI   Immunoassay of tacrolimus with monoclonal antibody having reduced
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     crossreactivity with tacrolimus metabolites
IN   Kasper, Kenneth G.; Jeong, Henry; Davalian, Dariush; Liu, Hshiou-ting;
     Miller, Paul L.; Williams, Denise L.
PA   Dade Behring Inc., USA
SO   PCT Int. Appl., 60 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     -----------------  ----  -------        ---------------  --------
PI   WO 2001009190      A2    20010209       WO 2000-US21036  20000802
     WO 2001009190      A3    20010816
         W: AU, JP
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE
     EP 1206499         A2    20020522       EP 2000-953792   20000802
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI, CY
PRAI US 1999-368010     A     19990803
     WO 2000-US21036    W     20000802


=> s FKBP conjugate
L3             1 FKBP CONJUGATE

=> d 123 ch ib abs

L3  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1994:462799  Document No. 121:82799  Conformational Changes of Rapamycin and
     Analogs upon Complexing with FKBP Associated with Activity: An Application
     of Second Derivative CD Spectroscopy. Chen, Yanqiu; Zhou, Peng; Berova,
     Nina; Inang, Hongzhi; Nakanishi, Koji; Failli, Amedeo; Steffan, Robert J.;
     Molnar-Kimber, Katherine; Caggiano, Thomas J. (Department of Chemistry,
     Columbia University, New York, NY, 10027, USA). Journal of the American
     Chemical Society, 116(6), 2683-4 (English) 1994. CODEN: JACSAT. ISSN:
     0002-7863.
AB   The CD spectra of FKBP conjugates of rapamycin and
     some of its analogs are reported. The neg. Cotton effect at 210 nm is
     enhanced in the conjugates and the Cotton effect of the triene absorption
     at .apprx.270 nm shows both enhanced vibrational structure and a sign
     inversion. The latter trend is clearer in the second deriv. CD and
     indicates that the triene moiety in the conjugates adopts a more rigid and
     planar conformation. The sign inversion of the Cotton effect reflects the
     chiral influence of the FKBP binding site. The CD curves of mixts. of
     FKBP with silylated or lysine-substituted rapamycin are superimposable on
     the summation CD curves of the free drug and FKBP.


=> s intracellular conjugate
L4             0 INTRACELLULAR CONJUGATE

=> d his

     (FILE 'HOME' ENTERED AT 10:37:33 ON 04 NOV 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 10:37:46 ON
     04 NOV 2002
L1          15256 S DRUG TARGETING
L2            813 S L1 AND INTRACELLULAR
L3             35 S L2 AND PROTEIN
L4             30 DUP REMOVE L3 (42 DUPLICATES REMOVED)
L5              5 S L4 AND FK506
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L6              5 DUP REMOVE L5 (0 DUPLICATES REMOVED)
L7             10 S FK506 CONJUGATE
L8              6 DUP REMOVE L7 (4 DUPLICATES REMOVED)
L9              0 S L4 AND CONJUGATE
L10             3 S L4 AND CONJUGATE
L11             3 DUP REMOVE L10  0 DUPLICATES REMOVED)
L12           791 S ESTRADIEN CONJUGATE
L13             0 S L12 AND BISPHOSPHONATE
L14             0 DUP REMOVE L13  0 DUPLICATES REMOVED)
L15            81 S ANDROGEN CONJUGATE
L16            38 DUP REMOVE L15  44 DUPLICATES REMOVED)
L17             1 S FKBP CONJUGATE
L18             1 S HSP90 CONJUGATE
L19             7 S RAPAMYCIN CONJUGATE
L20             7 DUP REMOVE L19  0 DUPLICATES REMOVED)
L21             0 S GELDANAMYCIN CONJUGATE
L22             1 S TACR KINASE CONJUGATE
L23             1 S FKBP CONJUGATE
L24             0 S INTRACELLULAR CONJUGATE

=> s (briesewitz r?/au  a crabtree g?/au or wandless t?/au)
L25          2294 (BRIESEWITZ R?/AU OR CRABTREE G?/AU OR WANDLESS T?/AU)

=> s l25 and conjugate
L26             7 L25 AND CONJUGATE

=> dup remove l26
PROCESSING COMPLETED FOR L26
L27             7 DUP REMOVE L26  0 DUPLICATES REMOVED)

=> d l27 1-7 ibib ab

L27 ANSWER 1 OF 7  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:284009  Document No.: PREV200200284009. Synthetic bifunctional molecules
     containing a drug moiety and presenter protein ligand. Briesewitz,
     Roger (1); Crabtree, Gerald R.; Wandless, Thomas;
     Kay, Gregory Thomas; Vogel, Kurt William. (1) Mountain View, CA USA.
     ASSIGNEE: The Board of Trustees of the Leland Stanford Jr. University; The
     Howard Hughes Medical Institute, Chevy Chase, MD, USA. Patent Info.: US
     6271210 April 10, 2001. Official Gazette of the United States Patent and
     Trademark Office Patents, (Apr. 10, 2001) Vol. 1257, No. 3, pp. No
     Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN:
     0098-1133. Language: English.
AB   Bifunctional molecules and methods for their use in the production of
     binary complexes in a host are provided. The bifunctional molecule is a
     conjugate of a drug moiety and a presenter protein ligand. The
     molecular weight of the bifunctional molecule is preferably less than
     about 5000 daltons, and the drug moiety may have a molecular weight of
     from about 50 to 2000 daltons. The drug moiety and presenter protein
     ligand may be covalently linked directly or through a linking group. The
     drug moiety binds to a drug target such as a protein and the presenter
     protein ligand binds to a presenter protein that is not the drug target
     such as extracellular or intracellular protein. Presenter proteins include
     peptidyl prolyl isomerase (FKBP), Heat Shock Protein 90 (Hsp90), steroid
     hormone receptors, cytoskeletal proteins, albumin and vitamin receptors.
     When the presenter protein is FKBP, ligands include FK506, rapamycin and
     cyclosporin A which may have an introduced functional group such as
     hydroxyl, amino, carboxyl, aldehyde, carbonate, carbamate, azide, thiol or
     ester for attaching the drug moiety. In the methods of use, an effective
     amount of the bifunctional molecule is administered to the host. The
     bifunctional molecule binds to the presenter protein to produce a binary
     complex such that the drug exhibits at least one of improved affinity,
     specificity or selectivity as compared to the corresponding free drug. The
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methods and bifunctional molecules find use in a variety of therapeutic applications.

L27 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
2001:[illegible] Document No. 134:[illegible] Bifunctional inhibitor molecules, their use in the disruption of protein-protein interactions and therapeutic applications. **Crabtree, Gerald R.**; Stankunas, Kryn; **Briesewitz, Roger; Wandless, Thomas** (The Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 2001[illegible] A1 [illegible], [illegible] pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO [illegible]-US[illegible] [illegible]. PRIORITY: US [illegible]-PV[illegible] [illegible].

AB Bifunctional inhibitor mols. and methods for their use in the inhibition of protein-protein interactions are provided. The subject bifunctional inhibitor mols. are **conjugates** of a target protein ligand and a blocking protein ligand, where these two moieties are optionally joined by a linking group. In the subject methods, an effective amt. of the bifunctional inhibitor mol. is administered to a host in which the inhibition of a protein-protein interaction is desired. The bifunctional inhibitor mol. simultaneously binds to its corresponding target and blocking proteins to produce a tripartite complex that inhibits the target protein-protein interaction. The subject methods and compns. find use in a variety of applications, including therapeutic applications.

L27 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
2001:[illegible] Document No. 134:[illegible] Targeted bifunctional molecules and therapies based thereon. **Briesewitz, Roger; Crabtree, Gerald R.; Wandless, Thomas** Board of Trustees of the Leland Stanford Junior University, USA. PCT Int. Appl. WO 2001[illegible] A1 [illegible], [illegible] pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO [illegible]-US[illegible] [illegible]. PRIORITY: US [illegible]-PV[illegible] [illegible].

AB Targeted bifunctional mols. and methods for their use are provided. The subject targeted bifunctional mols. are **conjugates** of a drug moiety and a targeting moiety, where these two moieties are optionally joined by a linking group. The bifunctional mols. are further characterized in that they exhibit a modulated biodistribution upon administration to a host as compared to a free drug control. The subject targeted bifunctional mols. find use in a variety of therapeutic applications. For example, a bifunctional mol. consisting of a drug moiety covalently joined to sulfisoxazole which is extensively bound by albumin, via an inert linking group is formed. When this bifunctional mol. enters the human circulation, it is bound by albumin which keeps the drug of interest in the extracellular environment.

L27 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
2001:[illegible] Document No. 134:[illegible] Drug **conjugates** with pharmacokinetic modulating moieties, and therapies based thereon. **Briesewitz, Roger; Crabtree, Gerald R.; Wandless,**

Thomas (The Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 2001035748 A1 20010525, 39 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 2000-US31701 20001117. PRIORITY: US 1999-PV166831 19991117.

AB Bifunctional mols. and methods for their use are provided. The bifunctional mols. of the invention are **conjugates** of a drug moiety and a pharmacokinetic modulating moiety, optionally joined by a linking group. The bifunctional mols. are further characterized in that they exhibit at least one modulated pharmacokinetic property upon administration to a host as compared to a free drug control. The subject bifunctional mols. find use in a variety of therapeutic applications.

L27 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS

2000:11661 Synthesis of an affinity-tagged flavonol and its use to probe the mechanism of flavonol-induced pollen germination.. Taylor, Lorraine P.; **Wandless, Thomas J.**; Tanaka, Hiroo; Miller, Keith; Stehmeyer, Michelle School of Molecular Biosciences, Washington State University, Pullman, WA, 99164-4234, USA . Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000, AGFD-156. American Chemical Society: Washington, D. C. English. 2000. CODEN: 69CLAA.

AB Maize and petunia pollen requires flavonols to germinate. Flavonol-deficient mutants are self-sterile because the pollen is unable to germinate but the defect can be reversed by adding kaempferol, a flavonol aglycon, to an in vitro suspension of pollen or to the stigma at pollination. Pollen germination response is sensitive (40% max. response), rapid (tube outgrowth within 5 min), and specific for flavonol aglycons. To elucidate the mechanism of kaempferol-induced germination, a small mol. probe incorporating a benzophenone photophore was synthesized using a variant of the Robinson annulation. A 7-step synthetic scheme produced 2-(3-benzoylphenyl)-3,5,7-trihydroxychromen-4-one in 17% yield. We have demonstrated that the pH responsive kaempferol deriv. is a substrate for flavonol 3-O-glucosyltransferase, the enzyme responsible for forming flavonol **conjugates** in pollen. Thus the compd. will be useful for detg. the active site residues involved in catalysis or substrate binding as well as identifying putative flavonol receptors in pollen.

L27 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS

1999:763888 Document No. 131:19929 Bifunctional molecules and therapies based thereon. **Briesewitz, Roger; Crabtree, Gerald R.**; **Wandless, Thomas**; Kay, Gregory Thomas; Wandel, Kurt William (The Board of Trustees of the Leland Stanford Junior University, USA). PCT Int. Appl. WO 9951084 A1 19991014, 67 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, EA, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 1999-US11296 19990521. PRIORITY: US 1998-85451 19980522.

AB Non-naturally occurring bifunctional **conjugates** Z-L-X (Z = ligand that binds to a specific presenter protein; X = drug moiety; L = optional linker) are provided such that upon entering a cell, Z can bind to its receptor protein (if present) and the effectiveness of X is thereby enhanced or inhibited, depending on the nature of the receptor for Z.

Thus, a bifunctional peptide (I) was prepd. which contained FK506 coupled to phosphotyrosyl-glutamyl-glutamyl-isoleucine (pYEEI), which binds to the SH2 domains of tyrosine kinases Fyn and Lck and to the N-terminal SH2 domain of phospholipase C.gamma. (PLC.gamma.). In the presence of FK506-binding protein 52 (FKBP52), I bound the Fyn SH2 domain with 7-fold increased affinity. This effect was reversed by FK506, and was not mimicked by FKBP12 despite the similar structure of its binding domain to that of FKBP52; the increase in affinity with FKBP52 was presumably based on favorable protein-protein interactions between the Fyn SH2 domain and FKBP52. On the other hand, formation of a FKBP12-I complex reduced the affinity of I for the PLC.gamma. SH2 domain but not for the Fyn or Lck SH2 domains, suggesting that formation of a binary complex may lead to unfavorable protein-protein interactions between the presenter protein and some targets but not other targets of the drug; therefore, formation of a complex between a bifunctional mol. and a presenter protein can be used to create specificity. The cell selectivity of a bifunctional **conjugate** may be enhanced if the formation of a binary complex reduces binding of the drug to all of its targets in a cell that contains the presenter mol.; if an organism has cells that contain the presenter protein and other cells that do not, the cells lacking the presenter protein will be more affected by the bifunctional **conjugate** than cells expressing the presenter. Similarly, conjugation of penicillamine (an alk. phosphatase inhibitor) to p-aminosalicylic acid (a ligand for albumin) via glycine modulated the inhibitory activity of penicillamine toward 4 isoforms of alk. phosphatase in the presence of 10% .mu.M serum albumin, but not toward 2 other isoforms.

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1996:418019 Document No. 124:76361 New method for identifying and evaluating biologically active molecules. Schreiber, Stuart L.; **Crabtree, Gerald R.**; Holt, Dennis A.; Koller, Mark J. Ariad Gene Therapeutics, Inc., USA). PCT Int. Appl. WO 9601613 A1 19960125, 82 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 1995-US14177 19951101. PRIORITY: US 1994-352645 19941101; US 1995-460800 19950605; US 1995-483266 19950607.

AB This invention concerns materials and methods for identifying an agent capable of effecting a biol. event in a cell, which event is (or can be) mediated by the assocn. of .gtoreq.2 protein mediators, at least one, and usually both, of which are endogenous. The method involves the steps of identifying a first compd. capable of binding to one of the protein mediators and a second compd. capable of binding to the other protein mediator. The 2 compds. then are joined covalently to one another to form a chem. inducer of dimerization (CID) that can bind to both mediators. Assay methods are provided for identifying the monomeric binding compds. and for evaluating and optimizing the CIDs produced from them. As one example, a CID was prepd. that is a **conjugate** of a HIV protease inhibitor (which binds to HIV protease) with a camptothecin analog (which binds to nuclear topoisomerase) and that can translocate HIV protease into the nucleus where it is inactive.

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